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ACUTE ANTERIOR POLIOMYELITIS

ORTHOPEDIC ASPECTS OF THE CALIFORNIA EPIDEMIC OF 1934

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LOS ANGELES

Anterior poliomyelitis made its appearance in California in 1875, when 2 cases were observed near Eureka. The disease first became epidemic at La Grande, near San Francisco, in 1898. A second epidemic, of relatively few cases, followed in San Francisco in 1902. In 1912 the disease became epidemic in Southern California; 531 cases were reported with 129 deaths. Sporadic cases were reported from time to time until 1925, when the disease again became epidemic, with a total of 821 cases and 144 deaths. Two years later, 1,298 cases were reported, with 224 deaths. During the epidemic of 1930, 1,003 cases were reported, with 157 fatalities.

The outbreak in 1934 showed a decided increase in the number of individual reported cases. This may have been due in part to the increasing alertness of the attending physicians, leading to a recognition of the disease in its preparalytic stage. A total of 3,333 cases, with 110 deaths, were reported by the State Board of Health, the fatality rate being 3.3 per cent.

During the epidemics already mentioned, there has been a steady shift of the incidence to the older age groups. In 1912, only 22 per cent of the patients were over 10 years of age. In 1925, 34.3 per cent were over 10, and in 1930, 40.6 per cent.[1]

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1. Dunshee, J. D., and Stevens, I. M.: Previous History of Poliomyelitis in California, Am. J. Pub. Health. **24**:1197 (Dec.) 1934.

In the epidemic of 1934 the incidence according to age was as follows:[2]

Age Group, Years	Cases	Percentage
Under 10	1,389	42.23
10 to 19	993	30.19
20 to 44	847	25.75
45 and older	60	1.83
Total, known ages	3,289	100.00
Age unknown	44	
	3,333	

GENERAL OBSERVATIONS

Geographic Distribution.—The more densely populated centers had the greatest incidence of the disease. Figure 1, a map of the state of California, illustrates this fact. Two thousand, one hundred and twenty cases were reported in Los Angeles County. A large proportion of these cases occurred in the metropolitan area of Los Angeles, the heaviest incidence being in the thickly populated Belvedere residential district, which lies east of the Los Angeles River. In Fresno County, approximately 200 miles north of Los Angeles on the island highway, 204 cases were reported. The city of Fresno is an overnight stopping point in transtate travel. The climate is warm and dry during the summer. The outbreak in the region of San Francisco Bay was next in importance, with 107 cases in Alameda, 123 in San Francisco and 41 in San Mateo counties. In Bakersfield, Orange, San Diego, Tulare, Santa Clara, San Bernardino and Sacramento counties considerable numbers of cases were reported from the more thickly settled sections.

Seasonal Morbidity.—One hundred cases observed in the orthopedic department of the Los Angeles General Hospital furnish the data for this report. They cannot serve to give a true cross-section of the epidemic because paralysis of a degree is at once presumed on a patient's admission to an orthopedic ward. Many patients were included in the lists of public health reports who presented the picture of a mild and rapidly vanishing illness.

The patients whose cases are included in this report readily group themselves into two classes, adult and juvenile. The affected children exhibited nothing out of the ordinary, while bizarre symptoms and signs characterized the disease in adults.

The epidemic of 1934, as exemplified by this series of cases, reached its height in June (fig. 2). The first patient of this series was seen in January, with an interval until May, when 21 patients were admitted to the hospital. Thirty-five were admitted to the hospital in June, 20 in July, 12 in August, 7 in September, 2 in October and 2 in November.

Pathology.—In the fatal case in this series autopsy disclosed marked generalized hyperemia of the spinal cord, slight edema and

2. The statistics were provided by the California State Department of Public Health.

injection of the cerebral meninges, gross muscular atrophy and hypostatic pneumonia. The pathologic diagnosis was subacute poliomyelitis. Microscopic sections are not yet available.

Van Wart, Courville and Hall [3] reported the results of their study of 15 cases of the epidemic of 1934 in which autopsy was performed.

Fig. 1.—The geographic distribution of cases of anterior poliomyelitis in the state of California during the epidemic of 1934.

Perivascular infiltration or cuffing was not confined to the motor areas but was noted to be equally distributed in the gray and white matter throughout the cord. Some of the vessels contained thrombi, causing infarctions. Other sections of the cord revealed areas of complete

3. Van Wart, Roy; Courville, Cyril, and Hall, E. M.: Am. J. Pub. Health **24**:1207 (Dec.) 1934.

destruction of cells, presumably due to infarction, with normal cells lying adjacent. Extensive cellular infiltration took place in certain cases, with disappearance of all nerve elements. An appreciation of the

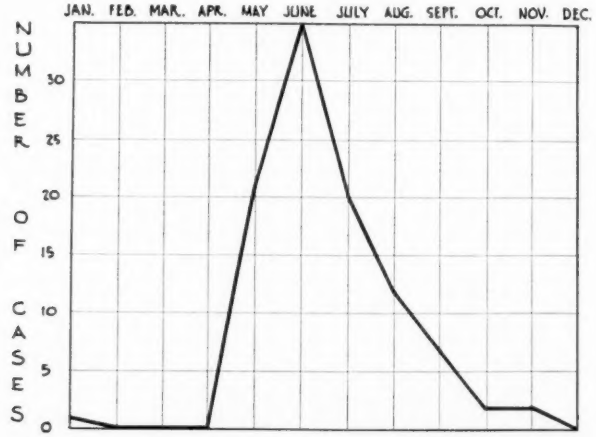

Fig. 2.—The seasonal morbidity during the epidemic of 1934.

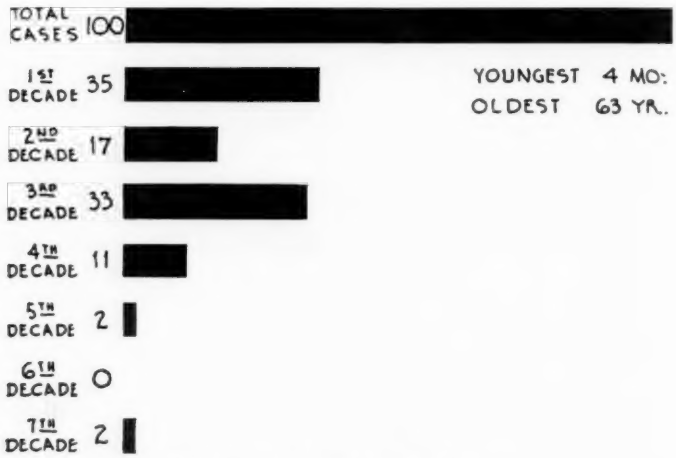

Fig. 3.—The incidence according to age.

pathologic changes serves to formulate an understanding of this disease with special regard to recovery.

Age.—The most striking fact revealed by a study of figure 3 is that 35 of the patients were in the first decade and 33 in the third decade

of life. Seventeen were in the second decade, 11 in the fourth, 2 in the fifth and 2 in the seventh.

Sex.—Sixty-four of the patients were females, and 36 were males. Four of the males were physicians and at the time of contracting the disease were engaged in the care of patients suffering from acute anterior poliomyelitis. Thirty-nine of the female patients were nurses in the Los Angeles General Hospital and for the most part were on duty in the wards for patients with poliomyelitis.

CLINICAL OBSERVATIONS

Onset and Complaints on Admission.—This study fails to reveal anything characteristic in the onset of this disease. It was abrupt, gradual or insidious. One nurse remained on duty at least six weeks after she had contracted the disease and reported her illness only because of increasing muscular weakness.

Headache was the most constant symptom, occurring as the only complaint in 49 patients. It was frequently (16 patients) associated with backache. Aching in the neck was the only complaint of 3 patients, backache of 4, headache, neckache and backache of 3, and backache and neckache of 2.

Nausea and vomiting were noted in 44 patients. Muscular weakness was a source of alarm to 20 patients; this was not necessarily confined to an extremity or to a single muscle group but was often described as general.

Pain in the extremities was not of infrequent occurrence and was noted in the lower extremities 15 times and in the upper extremities 9 times.

Nine patients were admitted to the hospital because of acute infections of the upper respiratory tract, with definite characteristics of anterior poliomyelitis developing later.

Complaints of limp, muscular twitching, earache, diarrhea, abdominal pain, dysphagia, photophobia, chills, irritability and drowsiness were noted on some occasions.

Findings on Admission.—Rigidity of the neck and back were the most important of the early findings. This condition was present in 59 of the patients when they were admitted to the hospital. Rigidity of the neck only was noted 3 times and of the back 5 times. Muscular weakness and tenderness were detected early in 43 patients. Weakness alone was present in 20 and tenderness in 18.

Fifteen patients showed a Kernig sign on admission and 16 a Brudzinski sign. These signs were present simultaneously in 3 patients. The Kernig and Brudzinski signs were demonstrated in 14 patients of 15 years or under and in only 4 patients over 25 years of age.

Lethargy was an occasional finding, being evident in 8 patients. Two patients were dyspneic on admission to the hospital; 4 had muscular twitching, and 1, definite dysphagia. Inequality of reflexes was noted in 12 patients, while in 3 the reflexes were hyperactive and in 3 they were not present.

Spinal Fluid.—Lumbar paracentesis to determine intraspinal pressure and withdrawal of fluid for examination were carried out on 76 patients. Lumbar puncture was not carried out on 24. The spinal fluid of 67 of the 76 patients showed some variation from the normal. The pressure or number of cells was increased, globulin was present or the colloidal benzoin reaction was positive (table 1). All the 9 patients with a

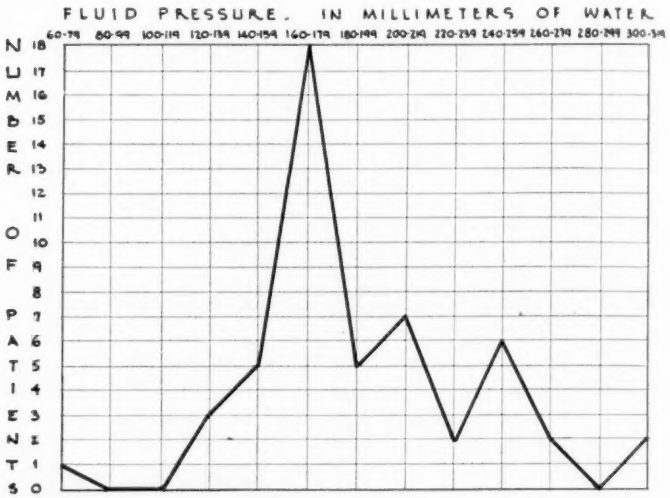

Fig. 4.—The spinal fluid pressure in millimeters of water.

normal spinal fluid had stiffness of the neck and back on admission to the hospital, and subsequently muscular weakness developed.

The spinal fluid pressure varied between 60 and 319 mm. of water. Eleven patients had a pressure of 175 mm., 6 of 200 mm. and 6 of 160 mm., comprising the largest group (fig. 4).

The cellular elements were increased in the spinal fluid of 31 patients. The number of cells per cubic millimeter varied from 12 to 2,200. Lymphocytes predominated in specimens of 27 patients. All the cells were polymorphonuclear leukocytes in 1 specimen. In the remaining 3 specimens there was a high polymorphonuclear cell count (fig. 5).

Character of Muscular Weakness.—Muscular weakness occurred in all 100 patients. The grade of weakness was uniform in some instances,

while in others the degree of paralysis varied with the individual affected muscles. Thirty-six patients suffered a slight degree of muscle weakness, 27 moderate and 23 severe. Severe and moderate paralysis were combined in 9 patients, severe and slight in 3 and moderate and slight in 2.

TABLE 1.—*Observations on the Spinal Fluid of 67 Patients* *

Case	Increased Spinal Fluid Pressure	Cells per Cubic Millimeter	Globulin	Colloidal Benzoin Reaction
1	+	0	Trace	Negative
2	+	0	0	0
3	+	0	0	+
4	+	0	0	0
5	0	+	1+	0
6	0	0	0	+
7	0	+	0	0
8	0	0	1+	0
9	+	+	1+	0
10	0	+	Trace	+
11	0	+	1+	+
12	0	+	1+	+
13	0	+	1+	0
14	0	+	1+	+
15	+	+	0	0
16	0	+	Trace	+
17	+	0	0	+
18	+	+	1+	+
19	0	+	0	+
20	+	0	0	0
21	0	0	0	+
22	0	+	2+	+
23	+	0	+	0
24	+	+	0	0
25	+	+	Trace	+
26	+	0	0	0
27	+	+	1+	0
28	+	+	0	+
29	+	0	0	0
30	+	+	0	0
31	+	+	0	0
32	+	+	0	+
33	0	+	1+	0
34	+	0	0	+
35	+	+	0	0
36	+	+	+	+
37	+	+	2+	+
38	+	+	0	+
39	+	0	Trace	0
40	+	+	2+	+
41	+	0	0	0
42	+	+	3+	+
43	0	+	Trace	+
44	+	+	Trace	+
45	+	0	Trace	+
46	+	+	0	+
47	+	+	1+	+
48	+	+	1+	+
49	+	+	2+	+
50	0	0	1+	0
51	+	0	1+	+
52	+	+	2+	+
53	+	0	0	0
54	+	0	Trace	0
55	+	+	1+	+
56	0	+	2+	+
57	+	0	0	0
58	+	0	0	0
59	+	0	Trace	+
60	0	0	Trace	0
61	+	0	0	+
62	+	+	+	+
63	+	+	1+	+
64	+	0	0	+
65	0	0	Trace	+
66	0	0	0	+
67	+	0	0	+

* There were abnormalities of the spinal fluid of 67 of the 76 patients whose spinal fluid was examined. Examination of the spinal fluid was not carried out on 24 patients.

The distribution of paralysis is indicated in table 2, which is intended to depict the muscular weakness as recorded at the height of the disease.

Condition in Adults.—Perhaps the most interesting clinical features of the epidemic of 1934 are to be found among the adult patients. The

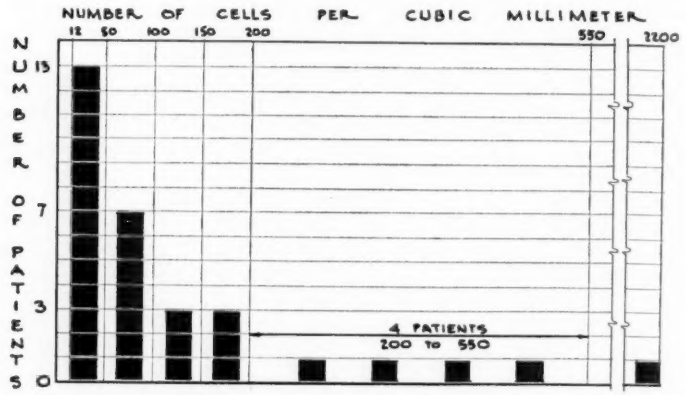

Fig. 5.—The number of cells per cubic millimeter of spinal fluid.

TABLE 2.—*Distribution of Paralysis*

Arms		**Legs**	
Right	2	Right	3
Left	3	Left	8
Right and left +		Right and left	15
Right leg	2		
Left leg	2	**Right and left +**	
Intercostals	1	Abdomen	7
Both legs	10	Diaphragm	1
Both legs, abdomen	5		
Left leg, abdomen	2	**Right alone**	
Both legs, face	1	Left side of face	1
Right leg, abdomen	1	Abdomen	3
Left leg, face	1		
Right alone +		**Both legs, both arms and trunk +**	
Right leg	5	Left side of face	1
Both legs	5	Abdomen	4
Abdomen	1		
Right side of face	1	Gluteal muscles	1
Left leg	2		
Left alone +			
Both legs	9		
Left leg, abdomen	2		
Left leg, left side of face, diaphragm, pharynx	1		

high incidence in the older age groups has already been noted. An unusual contagiousness was apparent in the extraordinary outbreak of the disease among nurses at the Los Angeles General Hospital, where more than 150 nurses were afflicted. Nearly 12 per cent of the hospital employees engaged in caring for the patients in the acute stage contracted the disease, in spite of all the precautionary technic of a well

ordered unit for the care of patients with communicable disease. Clinically the condition in adults was characterized by a predominance of sensory rather than of motor symptoms, by involvement of the joints in a considerable number of cases and by a remarkable tendency to recurrent exacerbation of acute symptoms.

The polyneuritic type of poliomyelitis has long been known as a rare form of the disease.[4] A small sporadic outbreak of a similar condition was described by Kennedy[5] in 1919, under the caption of infective neuronitis, and by Strauss and Rabiner[6] in 1930, who applied the term myeloradiculitis. A certain degree of doubt must be entertained as to the relationship of all these conditions to infantile paralysis of the usual type, since no specific diagnostic test is available.

Motor Symptoms: In all adults of this series, numbering 52 patients over 16 years of age, muscular weakness of a greater or less degree was noted. In a number of cases a marked degree of muscular weakness has persisted, without proportionate atrophy and without loss of tendon reflexes or electrical reactions. Involuntary muscular contractions, usually painful, were a troublesome complaint in certain cases. These consisted of twitching, clonic movements and cramps in the affected muscles. Muscular incoordination was occasionally a striking feature. In 1 case incoordination of the intercostal muscles and the diaphragm necessitated a short period of treatment in the respirator. Long after normal contractile power returned, the patients complained of persistent fatigue and lack of endurance.

Sensory Symptoms: Sensory rather than motor symptoms, however, dominated the picture in most of the adult patients. The outstanding complaint was pain in the back and in the extremities. In the cases of milder involvement this appeared not unlike the muscular tenderness commonly seen in typical poliomyelitis but more intense, more prolonged and likely to recur at intervals. In the cases of severe involvement the pain was intractable, excruciating and persistent for weeks or even months. Only partial relief could be obtained, even with large doses of opiates.

Invariably associated with the pain was local tenderness of the muscles, sometimes generalized but often confined to certain groups. In a number of cases the tenderness was most pronounced at the musculotendinous junctions. In a few cases there was definite tenderness of the nerve trunk.

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4. Wickman, Otto Ivar: Acute Poliomyelitis, Nervous and Mental Disease Monograph 16, New York, Nervous and Mental Disease Publishing Company, 1913.

5. Kennedy, Foster: Infective Neuronitis, Arch. Neurol & Psychiat. **2**:621 (Dec.) 1919.

6. Strauss, Israel, and Rabiner, Abraham: Myeloradiculitis: A Clinical Syndrome, Arch. Neurol & Psychiat. **23**:240 (Feb.) 1930.

Hyperesthesia, paresthesia and areas of anesthesia were also encountered, sometimes following the distribution of the nerve trunks and sometimes involving an entire extremity.

Vasomotor and Trophic Changes: Vasomotor and trophic disturbances were almost constant findings among the adult patients. Excessive sweating or abnormal dryness of the skin of the extremities, together with coldness and cyanosis, were the phenomena usually observed. In the cases of more severe involvement exfoliation of the skin of the affected extremities occurred, followed by glossy atrophy of the skin and atrophy of the subcutaneous tissue. Hypertrichosis and brittleness of the nails, with retardation or acceleration of growth, were often noted. It was the impression of many observers that a generalized disturbance of vasomotor control occurred in these patients, which best explained the emotional instability (occurring in 30 per cent of the cases) and the exacerbations of acute symptoms, to be described later.

TABLE 3.—*Distribution of Involvement in the Joints in the Adult Patients*

Joints	No. of Cases
Fingers and wrists	3
Shoulder, elbow, wrist and fingers	3
Shoulder, elbow and knee	1
Shoulder alone	1
Hip and knee	1
Both knees	1
Both knees and ankles	1
Multiple arthritis in all four extremities	1

Arthritis: A unique feature of this epidemic was the occurrence of inflammatory changes in and about the joints, which was observed in 34 per cent of the adult patients in the present series. In 10 per cent there were merely transitory but sharply localized pain and tenderness in the joints. Definite proliferative changes about the joints occurred, however, in the remaining 24 per cent. In the earlier stages of the disease, swelling and intense pain were present, sometimes with increased synovial fluid. Later, the acute inflammation was followed by fibrosis and contracture of the joint capsules, resulting in limited motion. Trophic changes, as described earlier, were usually present. In all these cases, muscular weakness occurred in the affected extremities.

The distribution of involvement of the joints in the more severe cases is set forth in table 3.

Exacerbations: The clinical course of the adult patient was marked in 52 per cent of the cases by a tendency to recurrent attacks of acute symptoms, usually consisting of pain in the back and extremities, headache, photophobia and severe vomiting. Increased intrathecal pressure was of course suspected and was sometimes found; but in many instances the spinal fluid pressure was not increased. These exacerbations of the

acute symptoms often occurred after the patient had apparently recovered and had returned to work. Although they sometimes occurred spontaneously, the attacks were more commonly precipitated by emotional strain or fatigue. In some cases they resulted from a too early attempt to institute physical therapy. In other cases they were apparently related to changes in the weather or to the onset of menstruation. The duration of these attacks varied from a day or two to several weeks, and the severity also varied from that of a mild indisposition to a prostrating illness, in which prolonged vomiting necessitated parenteral administration of fluids and dextrose for days at a time.

COMPLICATIONS

Among the children of this series the following complications occurred: One child survived an attack of pneumonia. In 1 secondary anemia developed. Two required treatment in the respirator. Mild scoliosis developed in 4. One suffered from an attack of osteomyelitis of the femur coincident with the onset of poliomyelitis.

The adults suffered from a somewhat different group of complications. Scoliosis has not been observed thus far. Disturbances of the menstrual cycle have been almost constant among the women. Other complications have occurred as follows:

	Cases
Thrombophlebitis of leg	2
Pneumonia	2
Cystitis	3
Renal calculus	2
Urinary incontinence	1

TREATMENT

All patients with acute poliomyelitis were hospitalized under quarantine in the Communicable Disease Unit of the Los Angeles General Hospital as soon as the diagnosis was established, and they were treated with absolute rest and early splinting of the affected regions, an orthopedic consultant being in attendance from the day the patient was admitted. Bradford frames were used, with attached and adjustable abduction arm splints and posterior wire leg splints.

In all cases in which the condition was recognized during the acute stage of the disease, convalescent serum, alternated with pooled adult serum, was administered intramuscularly and intravenously in amounts varying from 30 to 175 cc. The end-results in relation to serum therapy are indicated in table 4. Of the 14 patients with a severe degree of residual paralysis, all but 1 received serum. There was a definitely higher incidence of motor recovery, however, in the group that was treated with serum.

Immediately on release from quarantine, all patients showing a marked degree of paralysis were transferred to the orthopedic wards. Those with a milder degree of paralysis were cared for in convalescent wards and were discharged to the outpatient department.

Physical therapy was begun, whenever possible, as soon as the patient was released from quarantine. Warm salt baths were usually the first measure employed, followed by systematic muscle training as soon as muscular tenderness subsided. Among the children, this was nearly always possible in the fourth or fifth week. The adults, on the other hand, provided an entirely different problem. Except in those whose course followed that of the juvenile type of the disease, it was noted that

TABLE 4.—*End-Results in Relation to Serum Therapy*

	Received Serum (78)		No Serum (22)	
	Number	Per Cent	Number	Per Cent
Motor recovery	54	69.0	10	45
Persistent paralysis, mild	10	13.0	11	50
severe	13	16.7	1	5
Died	1	1.3	0	0

TABLE 5.—*Present Status of the One Hundred Patients*

	Children (48)		Adults (52)		Total	
	Number	Per Cent	Number	Per Cent	Number	Per Cent
Complete recovery	21	44	24	46	45	45
Complete motor recovery but still disabled	0	0	19	37	19	19
Muscular weakness still present	27	56	8	15	35	35
Slight degree	16	33	5	10	21	21
Severe degree	11	23	3	5	14	14
Died	0	0	1	2	1	1

persistent pain and tenderness prevented any active physical therapy in the early weeks of the illness. Attempts to begin even the gentlest treatment, such as immersion for a few minutes in a warm salt bath, often precipitated a violent exacerbation of symptoms; and it soon became evident that the only measures that could be safely applied at this stage were gentle massage and assisted active movements for the affected joints. These measures were carried out in the ward, without removing the patient from the bed. Eventually, after many weeks, the patients became able to tolerate underwater therapy, which has been of great assistance in restoring function.

The sensory symptoms in adults have been peculiarly resistant to medication. The most effective measures have been absolute rest, including immobilization of all four extremities, good nursing care and

parenteral administration of fluid and dextrose in cases of excessive vomiting

Spinal puncture relieved severe headache in some cases, and it was felt that retention enemas of a hypertonic solution of magnesium sulfate or sodium chloride were also of some value during acute exacerbations, but the reaction to these procedures was not constant.

PRESENT STATUS

The progress of the 100 patients up to May 15, 1935, is set forth in table 5. Fourteen of the group were still severely paralyzed, and recovery seemed doubtful. The remainder were expected eventually to make a good functional recovery.

In the group of 19 adults who were still disabled, although fully recovered from all objective evidence of muscular weakness, the following symptoms and findings are held responsible for disability:

	Cases
Headache	8
Pain in one or more limbs	8
Fatigue	7
Arthritis	7
Emotional instability	3
Renal calculus	2

COMMENT

The striking difference between the condition in the children and that in the adults in this series arouses at once a doubt as to the correctness of the diagnosis. Were we dealing with two different diseases, or did the same virus produce a different clinical picture in adult patients?

In support of the contention that the condition in adults was an atypical form of true anterior poliomyelitis, the following considerations are submitted:

1. The cases occurred at the height of an epidemic in which a majority of cases were instances of typical poliomyelitis affecting children.

2. Most of the adult patients in this series were nurses engaged in caring for patients with poliomyelitis in the acute stage.

3. Muscular weakness was noted by competent observers in every case; and in 35 cases, paralysis has persisted up to the time of writing.

The criticism has also been made that many of the late symptoms complained of by the adult patients may have been of functional origin. The cases of milder involvement with many subjective complaints if encountered individually might well give this impression. The striking uniformity of the clinical picture presented by the patients,

however, and the prostrating severity of the symptoms in many cases led most observers to believe that an organic basis for the complaints was present in virtually every case.

SUMMARY

The 1934 epidemic of poliomyelitis was more extensive than any previous outbreak in California and was relatively mild, the fatality rate being 3.3 per cent.

Peculiar features of this epidemic were the unusual communicability of the disease, the early peak (in June) and the large number of adults affected.

In children, the disease followed the usual clinical course.

Among the adults, an atypical form of the disease was observed, in which sensory, vasomotor and arthritic symptoms predominated and recurrent exacerbations of acute symptoms occurred.

ABSTRACT OF DISCUSSION

DR. WILLIAM H. PARK, New York: The epidemic of poliomyelitis in Los Angeles was most interesting from the medical standpoint. It is doubtful whether all the suspected cases were instances of poliomyelitis.

During the last few years most people lost faith in the use of antipoliomyelitis serum in the treatment of poliomyelitis in the preparalytic stage. This is largely due to the fact that in several outbreaks only a portion of the children were given the serum, while the others were used as controls. Dr. Kramer and Dr. Aycock started a parallel series of tests in two hospitals, in which only one half of the patients were treated with antiserum. At the end of the epidemic there were no apparent differences between the results in the untreated and those in the treated patients. In New York, where nearly 1,000 patients in the preparalytic stage were divided so that about one half were untreated and a little more than half were treated, no differences were noted. It will be noted that where control cases have been used serum is usually no longer employed. Where control cases have not been used, physicians are giving the serum.

Dr. Brebner had an opportunity in 1931 to administer the antivirus serum as a preventive measure. It seemed to be of value, but more cases must be observed before one can be sure. Of the group treated, poliomyelitis developed in only 1 and was very mild, while of twice the number of untreated children poliomyelitis developed in 13 or 14 after 1,200 were immunized.

There are two vaccines; of one Dr. Kolmer will speak; the other was developed by Dr. Brodie. Dr. Kolmer's is virulent for monkeys but apparently not for human beings. According to Dr. Brodie's method, the vaccine is treated with a solution of formaldehyde, left for from six to eight hours in the icebox and then used. It is known that two injections of vaccine will produce a definite humoral immunity in infants or children. If there is the slightest immunity already present, even one injection will establish it. As those who have no immunity are those most liable to the disease, I think that two injections should be given.

During this winter in Kern County, Calif., there was a small epidemic. About 70 cases of poliomyelitis were reported. The vaccine was given to about

1,500 young persons. Poliomyelitis did not develop in any of the treated children. There is a possibility, therefore, that the vaccine did good. It will be interesting to administer the vaccine on a larger scale this summer. I hope to give it free of charge in certain states where it is needed.

DR. PHILIP LEWIN, Chicago: Up to the time that I read Dr. Wilson's paper my impression had been that the usual number of cases of poliomyelitis occurred in Los Angeles and that coincidentally another disease became epidemic.

The significant features which were in contrast to poliomyelitis, as I understand it, were the following: (1) too early occurrence of the peak of the epidemic, i. e., in May and June; (2) the high incidence of communicability; (3) the high incidence in adults—4 physicians and 39 nurses; (4) the atypical course in adults; (5) the mildness of the attack; (6) the marked degree of muscle weakness without proportionate atrophy and without loss of tendon reflexes or electrical reactions, and (7) the recurrences.

There is probably a high incidence of infection in cases of poliomyelitis but a low incidence of contagion-producing paralysis. One may have a subclinical form without cerebrospinal infection.

Examination must be made deliberately. A proper examination during the systemic or preparalytic stage requires about one hour. It is practically impossible for health officers, under the present regimen and especially during an epidemic, to spend that much time.

One of the important findings was "spotty motor paralysis" without sensory paralysis. Two of the most important reflexes during the early stage are the abdominal and the cremasteric reflex. If a physician sees a patient in the morning with active or hyperactive knee jerks and the knee jerks cannot be elicited at the end of that day or the next, this is in favor of a diagnosis of infantile paralysis.

During the systemic phase and the preparalytic stage, the differential diagnosis must include epidemic meningitis and tuberculous meningitis. Encephalitis must be distinguished from an early stage of bulbar poliomyelitis. Acute rheumatic fever and articular rheumatism must be differentiated. Polyneuritis is associated with sensory disturbances. Osteomyelitis and scurvy each have their characteristic symptoms. Central pneumonia with toxic encephalitis may present some difficulty in diagnosis. Diphtheritic neuritis may have to be differentiated.

One of Dr. Legg's patients, who had 600 cells per cubic millimeter of spinal fluid, proved to have mumps.

In children and adults one should inject intraspinally 5 cc. less of convalescent serum than the amount of fluid removed, which is usually 25 cc., and intravenously 60 cc. In adults one should inject about 20 cc. intraspinally and 160 cc. intravenously. Serum should not be given intraspinally in cases of bulbar poliomyelitis or to patients with a normal spinal fluid cell count. From 1916 to 1931 the reports on serum therapy were favorable. But since the report of Park, the reverse has been true. It may well be that the preparation, dosage and administration are inadequate. In the absence of a proved specific and in the absence of proof of its ineffectiveness, I shall continue to recommend the use of convalescent serum during the preparalytic stage. One cannot look for significant progress in the treatment of poliomyelitis except from biologic sources, such as vaccines and serums.

The operations for the residual effects of poliomyelitis are well standardized. New procedures will be designed for special conditions, but the most important attack of the future will probably be from the biologic standpoint.

It is hoped that by the use of protective vaccines, early diagnosis and the prompt administration of convalescent serum paralysis can be eliminated in the disease called anterior poliomyelitis.

DR. JAMES P. LEAKE, Washington, D. C.: I agree with Dr. Wilson's conclusions that the matter of the exact identity of the condition in some of these cases in adults should be left open at present. His analysis from the point of view of an orthopedic surgeon, however, leaves the impression that the condition was probably atypical poliomyelitis, in spite of some evidence to the contrary. I want to say merely that the condition as I observed it in Los Angeles was not at all encephalitic, and I do not think that it corresponded to the Australian X disease.

DR. MAURICE BRODIE, New York: I just mentioned to Dr. Leake that I thought this disease resembled the Australian X disease. I thought that there was evidence of involvement of the upper motor neurons that accounted for some of the unusual symptoms in the cases of poliomyelitis in adults. For example, there was a certain amount of emotional upset, and the paralysis seemed to resemble involvement of the upper motor neurons, with no atrophy to speak of. However, the authors did not mention whether there was any spasticity. The Australian X disease likewise included involvement of the upper motor neurons and perhaps involvement of the autonomic nervous system, and it is known that in some of the cases the disease was poliomyelitis, for Breinl transmitted the disease to monkeys, although others had shown by experiments in sheep that the disease in some patients was encephalitis. Poliomyelitis as it is usually known involves the cord and some of the brain stem, but in the cases in California it may have involved the higher centers. The sensory manifestations were not altogether out of gear. They have been reported, and in my experimental study of monkeys I have noted involvement of the posterior ganglions. Some of the neurons of the lumbar and cervical ganglions showed nearly all the cells to be destroyed.

Dr. Lewin showed a chart of systemic reactions and indicated that the virus travels from the nose to the blood and thence to the central nervous system. However, the virus most likely travels along nerve paths, and so virus is fixed in the nervous system. To give serum at any stage would be analogous to treating diphtheria four or five days after infection is established, when the toxin is fixed to the tissues and cannot be dislodged with an antibody.

UNCOMPLICATED AURICULAR FIBRILLATION AND AURICULAR FLUTTER

FREQUENT OCCURRENCE AND GOOD PROGNOSIS IN PATIENTS WITHOUT OTHER EVIDENCE OF CARDIAC DISEASE

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Auricular fibrillation and auricular flutter are common and well recognized disorders of cardiac rhythm. Less well appreciated, however, is their occurrence in persons without other signs of cardiac disease. To emphasize the frequency of this occurrence and to demonstrate its good prognosis constitute the main objects of the present communication.

REVIEW OF THE LITERATURE

Premature beats [1] and paroxysmal tachycardia [2] have long been known to occur in healthy persons. That auricular fibrillation may arise in a heart previously healthy was first pointed out by Gossage and Hicks [3] in 1913, although Fox [4] and Mackenzie [5] a few years before noted no evidence of cardiac disease in several of their cases. Since these early communications there have appeared in the literature numerous reports of auricular fibrillation occurring in persons with a clinically normal heart as a result of varied stimuli—toxic, traumatic and reflex—and without any obvious cause. The following list has been

From the cardiographic laboratory and cardiac clinics of the Massachusetts General Hospital.

1. Mackenzie, J.: Diseases of the Heart, ed. 3, New York, Oxford University Press, 1913.

2. Bristowe, J. S.: On Recurrent Palpitations of Extreme Rapidity in Persons Otherwise Apparently Healthy, Brain **10**:164, 1888.

3. Gossage, A. M., and Hicks, J. A. B.: On Auricular Fibrillation, Quart. J. Med. **6**:435, 1913.

4. Fox, G. H.: The Clinical Significance of Transitory Delirium Cordis, Am. J. M. Sc. **140**:815, 1910.

5. Mackenzie, J.: Digitalis, Heart **2**:273, 1910-1911.

assembled to show many interesting examples noted in the literature and in our own cases:

1. Toxic factors
   - A. Infections
     - Pneumonia [6]
     - Influenza [7]
     - Osteomyelitis [6b]
     - Gastro-enteritis [6b]
     - Malarial chill [8]
     - Pelvic abscess [8]
   - B. Drugs
     - Epinephrine [9]
     - Digitalis [10]
     - Acetylsalicylic acid [11]
     - Ether [12]
   - C. Other chemical agents
     - Alcohol [13]
     - Tobacco [14]
     - Hydrogen sulphide [15]
     - Arsenic [16]
     - Gas (CO) in a refrigerator car [12b]
     - Gasoline fumes (?) [12b]
   - D. Diabetic coma [17]

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6. (*a*) Krumbhaar, E. B.: Transient Auricular Fibrillation, Arch. Int. Med. **18**:263 (Aug.) 1916. (*b*) Parkinson, J., and Campbell, M.: Paroxysmal Auricular Fibrillation: A Record of Two Hundred Patients, Quart. J. Med. **23**:67, 1930. (*c*) Cases in this series.

7. Patterson, R. V.: Transient and Recurrent Auricular Fibrillation, J. A. M. A. **82**:453 (Feb. 9) 1924.

8. Instances of auricular fibrillation of this type occurred in our series.

9. Hume, W. E.: The Action of Adrenaline Chloride on the Human Heart, Quart. J. Med. **21**:459, 1927. Smith, F. M., and Moody, W. B.: The Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, Arch. Int. Med. **32**:192 (July) 1923.

10. Brams and Gaberman, quoted by McEachern and Baker.[29f]

11. Dutt Gupta, A. K.: A Case of Auricular Fibrillation After Aspirin, Indian M. Gaz. **63**:531, 1928.

12. (*a*) Levine, S. A.: Acute Cardiac Upsets Occurring During or Following Surgical Operation, J. A. M. A. **75**:795 (Sept. 18) 1920. (*b*) Fowler, W. M., and Baldridge, C. W.: Auricular Fibrillation as the Only Manifestation of Heart Disease, Am. Heart J. **6**:183, 1930. (*c*) Fox.[4]

13. (*a*) Wolferth, C. C.: Intermittent Auricular Fibrillation, Arch. Int. Med. **36**:735 (Nov.) 1925. (*b*) Fowler and Baldridge.[12b] Patterson.[7] Cases also occurred in our series.

14. Laslett, E. E.: Notes on Four Cases of Paroxysmal Tachycardia, Quart. J. Med. **15**:18, 1921.

15. Robinson, G. C.: Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphide Poisoning, J. A. M. A. **66**:1611 (May 20) 1916.

16. Cassidy, M., quoted by Cowan.[21]

17. Borg, J. F.: Diabetic Acidosis: Etiological Factor in Production of Auricular Fibrillation, Minnesota Med. **11**:580, 1928.

2. Trauma
   A. Injuries
      1. To the head [18a]
      2. To the chest [18b]
   B. Shock
      Electric [19]
   C. Instrumentation to the ear [12b]
   D. Burns [8]
3. Reflex
   A. Appendicitis [13a]
   B. Gallbladder colic [20]
   C. Peptic ulcer [20a]
   D. Indigestion and overeating [21]
   E. Cough [3]
   F. Vomiting [8]
   G. Operation [8]
4. Exertion [22]
5. Nervous disturbance
   A. Excitement [23]
   B. Emotion [24]
6. Miscellaneous
   Kyphoscoliosis [25]
7. No apparent cause [26]

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18. (*a*) Bramwell, C.: Can a Head Injury Cause Auricular Fibrillation? Lancet **1**:8, 1934. (*b*) Kahn, M. H., and Kahn, S.: Cardiovascular Lesions Following Injury to the Chest, Ann. Int. Med. **2**:1013, 1929.

19. (*a*) Jaksch-Warthenhorst, R., and Rihl, J.: Vorhofsflimmern nach elektrischem Trauma, Ztschr. f. d. ges. exper. Med. **50**:110, 1926. (*b*) Hay, J., and Jones, H. W.: Trauma as a Cause of Auricular Fibrillation, Brit. M. J. **1**:559, 1927. (*c*) Laslett, E. E.: A Paroxysm of Auricular Fibrillation Caused by Electric Shock, ibid. **1**:919, 1927.

20. (*a*) Felderbaum, D., and Finesilver, B.: Transient Auricular Fibrillation in Abdominal Diseases, Am. Heart J. **2**:416, 1927. (*b*) Footnote 8.

21. Cowan, J.: The Causes of Auricular Fibrillation, Quart. J. Med. **22**:237, 1929.

22. Reid, W. D.: Auricular Fibrillation in an Apparently Normal Heart, Boston M. & S. J. **197**:1213, 1927. Fowler and Baldridge.[12b] Hay and Jones.[19b] Wolferth.[13a] Laslett.[14] Cases also occurred in our series.

23. Semerau, M.: Ueber Rückbildung der Arhythmia perpetua, Deutsches Arch. f. klin. Med. **126**:161, 1918. Fowler and Baldridge.[12b] Hay and Jones.[19b] Laslett.[14] Footnote 8.

24. Heitz, J.: La forme paroxystique de l'arythmie complète, Ann. méd. **1**:483, 1914. Mouquin, M.: Les formes paroxystiques de l'arythmie complète, Médecine **8**:420, 1927. Footnote 8.

25. Boas, E. P.: The Cardiovascular Complications of Kyphoscoliosis with Report of a Case of Paroxysmal Auricular Fibrillation in a Patient with Severe Scoliosis, Am. J. M. Sc. **166**:89, 1923.

26. Levine, S. A.: Auricular Fibrillation: Some Clinical Considerations, Am. J. M. Sc. **154**:43, 1917. Smith, F. J., and Clark, N. E.: Quinidine in the Treatment of Auricular Fibrillation—Established, Paroxysmal, and Transient, Arch. Int. Med. **36**:839 (Dec.) 1925. Parkinson and Campbell.[6b]

Fowler and Baldridge,[12b] reemphasizing the association of varied stimuli, collected the reports of 35 such cases from the literature, to which they added 10 of their own. The most comprehensive review of the subject of paroxysmal auricular fibrillation has been contributed by Parkinson and Campbell [6b] in their report of 200 cases, in 15 per cent (30 cases) of which there was no evidence of cardiac disease. Recently, Weisman [27] and Gold, Otto and Satchwell [28] have mentioned several cases without giving any details, and Bramwell [18] has recorded the case of a healthy man in whom fibrillation followed trauma to the head. Discussions on the possible etiologic factors and mechanisms involved in the genesis of fibrillation have been presented by many authors [29] and need not be reviewed here. Among others, Yater,[30] and Mohler and Crawford [31] have clearly demonstrated that there is no pathologic change in the heart characteristic of auricular fibrillation.

The view that auricular flutter may occur with no other sign of cardiac disease was first advanced by Ritchie [32] in 1914, but Lewis,[33] Mackenzie [1] and Cowan [34] had previously reported cases in which no evidence of cardiac disease was shown. Similarly, a case of Parkinson and

27. Weisman, S. A.: Auricular Fibrillation: Ambulatory Treatment with Quinidine, Arch. Int. Med. **49**:728 (May) 1932.

28. Gold, H.; Otto, H. L., and Satchwell, H.: The Use of Quinidine in Ambulatory Patients for the Prevention of Paroxysms of Auricular Fibrillation and Auricular Flutter, Am. Heart J. **9**:219, 1933.

29. (*a*) Robinson, G. C.: Paroxysmal Auricular Fibrillation, Arch. Int. Med. **13**:298 (Feb.) 1914. (*b*) Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, ed. 3, London, Shaw & Sons, Ltd., 1925, p. 387. (*c*) Carter, E. P.; Andrus, E. C., and Dieuaide, F. R.: A Consideration of the Cardiac Arrhythmias on the Basis of Local Circulatory Changes, Arch. Int. Med. **34**:669 (Nov.) 1924. (*d*) de Boer, S.: Nature et origine de la fibrillation, Arch. d. mal. du cœur **20**:137, 1927. (*e*) Andrus, E. C., and Carter, E. P.: The Refractory Period of the Normally Beating Dog's Auricle with a Note on the Occurrence of Auricular Fibrillation Following a Single Stimulus, J. Exper. Med. **51**:357, 1930. (*f*) McEachern, D., and Baker, B. M.: Auricular Fibrillation: Etiology, Age, Incidence, and Production by Digitalis Therapy, Am. J. M. Sc. **183**:35, 1932.

30. Yater, W. M.: Pathologic Changes in Auricular Fibrillation and in Allied Arrhythmias, Arch. Int. Med. **43**:808 (June) 1929. Gossage and Hicks.[3] Fowler and Baldridge.[12b] Bramwell.[18] Patterson.[7] Felberbaum and Finesilver.[20a] Cowan.[21]

31. Mohler, H. K., and Crawford, B. L.: Pathological Changes in the Heart in Auricular Fibrillation, Am. J. M. Sc. **187**:171, 1934.

32. Ritchie, W. T.: Auricular Flutter, London, E. W. Green & Son, Ltd., 1914.

33. Lewis, T.: Observations on a Curious and Not Uncommon Form of Extreme Acceleration of the Auricle: Auricular Flutter, Heart **4**:171, 1912-1913.

34. Cowan, J.: Diseases of the Heart, Philadelphia, Lea & Febiger, 1914, p. 207.

Mathias[35] and several instances by Blackford and Willius[36] were recorded in which toxic or infectious factors were presumably responsible for flutter in hearts probably otherwise normal. Single instances without an obvious cause, though in several the paroxysms were precipitated by exertion, have been presented by Keating and Hajek,[37] Scott,[38] Gallavardin, Bonnamour and Bernheim,[39] Sprague and White[40] and Bourne.[41] Two patients were observed by Mackenzie[42] (one previously reported by Lewis) over forty years after what was probably the first appearance of paroxysms of auricular flutter. Parkinson and Bedford[43] in their review of fifty-two cases of flutter found no evident cardiac disease in five patients followed for many years and concluded that "occasionally like paroxysmal tachycardia and extrasystoles, flutter is the only evidence of cardiac abnormality—no more than a functional disturbance."

Nervous influences, sympathetic (accelerator) stimulation, combined with lack of vagal inhibition, either alone[32] or with an accompanying pathologic change in the auricular musculature,[37] have been proposed to explain the production of flutter in these patients.

From a consideration of the literature it is thus obvious that the concept of severe disturbances of cardiac rhythm occurring in the absence of other manifestations of cardiac disease is not new. Wilson, Wishart, MacLeod and Barker[44] have reported that even ventricular tachycardia, an arrhythmia usually dependent on serious cardiac pathologic change, may be present with no other sign of cardiac disease.

35. Parkinson, J., and Mathias, H. H.: Tachycardia of Auricular Origin and Flutter with Phasic Variation in Auricular Rate and in Conduction, Heart **6**:27, 1915.

36. Blackford, J. M., and Willius, F. A.: Auricular Flutter, Arch. Int. Med. **21**:147 (Jan.) 1918.

37. Keating, J. H., and Hajek, J.: Auricular Flutter with Report of Cases, Am. J. M. Sc. **164**:656, 1922.

38. Scott, R. W.: A Case of Auricular Flutter with Paroxysmal Attacks of 1:1 Conduction, J. A. M. A. **79**:1984 (Dec.) 1922.

39. Gallavardin, L.; Bonnamour, S., and Bernheim, M.: Un cas de flutter 1:1, Arch. d. mal. du cœur **17**:342, 1924.

40. Sprague, H. B., and White, P. D.: Auricular Flutter: Report of a Case of Five Years' Duration with Spontaneous Restoration to Normal Rhythm, J. A. M. A. **90**:1772 (June 2) 1928.

41. Bourne, G.: Three Cases of Paroxysmal Auricular Flutter, Lancet **1**:686, 1933.

42. Mackenzie, J.: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925.

43. Parkinson, J., and Bedford, D. E.: The Course and Treatment of Auricular Flutter, Quart. J. Med. **21**:21, 1927.

44. Wilson, F. N.; Wishart, S. W.; MacLeod, A. G., and Barker, P. S.: A Clinical Type of Paroxysmal Tachycardia of Ventricular Origin in Which Paroxysms Are Induced by Exertion, Am. Heart J. **8**:155, 1933.

Levine and Sturgis [45] have long emphasized the importance of auricular fibrillation, particularly in its transient form, as a sign of unrecognized hyperthyroidism. Similarly, Wohl [46] has mentioned hyperthyroidism masked as auricular flutter.

During the past twenty years few significant follow-up studies [47] have appeared demonstrating the actual prognosis in these cases of auricular fibrillation or of auricular flutter. We have observed a large group of patients, and have deemed it worth while to report on the cases after a sufficient number of years had elapsed to make the study of value.

MATERIAL AND OBSERVATIONS

This report comprises observations on 49 cases of auricular fibrillation and 7 cases of auricular flutter in none of which definite evidence of cardiac disease was demonstrated by history, physical examination, roentgen study or electrocardiograms of the patients. Two cases are included in both groups [48] because the patients presented at different times paroxysms of both disorders. Automatically excluded were those cases in which the patient offered any sign of the common factors usually held responsible for these forms of arrhythmia, namely, rheumatic fever, disease of the coronary arteries, hypertension and hyperthyroidism. No case was rejected because of age or the presence of peripheral arteriosclerosis.

The majority of cases were derived from private practice, and an idea of the incidence of such cases can be gained from the following data: Of 5,000 patients seen in consultation for some complaint relative to the heart, 583 (11.6 per cent) had auricular fibrillation and 38 (0.76 per cent) auricular flutter. In 36 (6.2 per cent) of the former and 5 (13.2 per cent) of the latter these disorders were not accompanied by detectable cardiac disease.

For reasons of simplicity and clarity it seems best that we present the observations on the two groups of auricular fibrillation and auricular flutter separately.

AURICULAR FIBRILLATION

In the group of 49 cases of auricular fibrillation the diagnosis was made by electrocardiograph in 25, through observation of an attack by a physician in 21 and on the basis of a typical history of paroxysmal attacks of irregular prolonged palpitation with sudden onset and offset in the remaining 3.[49]

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45. Levine, S. A., and Sturgis, C. C.: Hyperthyroidism Masked as Heart Disease, Boston M. & S. J. **190**:233, 1924. Levine, S. A.: Unrecognized Hyperthyroidism Masked as Heart Disease, Ann. Int. Med. **4**:67, 1930.

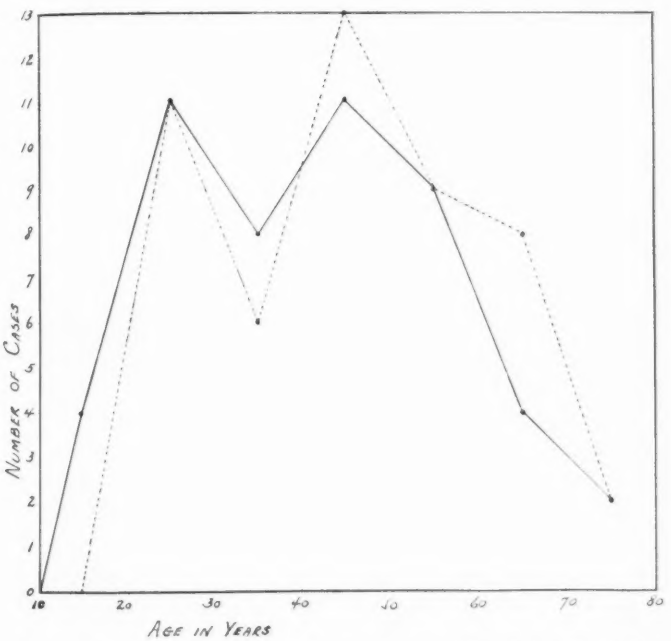
46. Wohl, M. G.: Hyperthyroidism Masked as Hypertension: Auricular Flutter, M. Clin. North America **17**:751, 1933.

47. Mackenzie.[1] Parkinson and Campbell.[6b] Mackenzie.[42] Parkinson and Bedford.[43]

48. Cases 23 and 24 of auricular fibrillation correspond to cases 6 and 4 of auricular flutter.

49. Case 12 has been previously reported by Wolff, Parkinson and White (Am. Heart J. **5**:685, 1930). The patients in cases 1, 2 and 14 are brothers and will be reported on in detail by one of us (L. W.).

The ages varied from 21 to 75 years, and when classified according to age at onset 23 patients were under 40. Forty-four were men and 5 were women. Eighty per cent of the men were engaged in occupations requiring mental as opposed to physical effort; 30 per cent were physicians. The women were chiefly housewives. The most frequent symptom of paroxysmal fibrillation was irregular, rapid palpitation, abrupt in onset, variable in duration and sudden in termination. Less commonly encountered were weakness, dizziness, faintness, nervousness and pain, precordial or substernal. In its established form fibrillation was usually present without palpitation save on effort. No patient showed any evidence of



Distribution according to age of forty-nine cases of auricular fibrillation with no other evidence of cardiac disease. The solid line indicates the age at onset, and the dotted line, the age of the patient when examined.

cardiac disease on physical examination. An interesting and possibly significant finding was the presence of premature beats between paroxysms of auricular fibrillation in 20 patients. Several patients presented slight murmurs, all systolic, mitral, pulmonic or aortic, to which no definite organic importance could be attached. Roentgen studies were performed on 18 patients at the first observation, and electrocardiographic confirmation of auricular fibrillation was obtained in 25 instances. Minor degrees of left axis deviation with angles varying from 0 to minus 15 degrees were present in 5 instances, in at least 3 of which the deviation was associated with a transverse position of the heart due to a high diaphragm.

TABLE 1 (Subgroup 1).—*Data on Patients with Auricular Fibrillation with no Other Evidence of Cardiac Disease (Age at Onset Under 40 Years)*

Case and Sex	Age at Onset	Age When Examined	Type	No. of Attacks	Duration of Attacks	Probable Precipitating Cause	Possible Contributory Factors	Diagnosed by	Years Followed	Years Since Onset	Age at Present	Follow-Up	Follow-Up Data*
1 M	8(?)	26	Established	3	? years	Alcohol (2)	.....	Electrocardiogram	7	25	33	Letter	Prolonged fibrillation, converted to normal rhythm; two recurrences owing to alcohol; permanent fibrillation 1 year ago; now well, healthy, athletic; no symptoms except palpitation on exertion
2 M	14(?)	24	Established	2	? years	.....	.....	Electrocardiogram	6	16	30	Letter	Prolonged fibrillation, converted to normal rhythm; soon reverted to permanent fibrillation; now well, healthy, athletic; no symptoms except palpitation on exertion
3 M	18	23	Paroxysmal	3	4 to 8 days	Exertion (1) (running)	Garage work; fatigue	Electrocardiogram	2	7	25	In person	Healthy, active, athletic; no symptoms; no paroxysms for 2 years; heart normal
4 F	19	48	Paroxysmal	3	1 week to ? year	.....	.....	Electrocardiogram	4	33	52	In person	Well; obese; works hard; no symptoms; no paroxysms for 2 years; heart normal; electrocardiogram showed inverted lead III
5 F	21	21	Paroxysmal	1	8 hours	Vomiting	Coryza; pregnancy	Physician	6	6	27	Letter	Excellent health; occasional palpitation from excessive smoking or strenuous exertion; no other symptoms
6 M	23	23	Paroxysmal	1	12 hours	Exertion (running)	Fatigue	Physician	11	11	34	Letter	Healthy; active; no symptoms; no paroxysms for 11 years; passed several rigid physical examinations
7 M	23	28	Paroxysmal	6	½ to 4 hours	Emotion (fear)	.....	Electrocardiogram	6	11	34	In person	Occasional paroxysm; otherwise healthy, active, athletic
8 M	23	25	Paroxysmal	3	36 hours to ? months	Exertion (1)	.....	Electrocardiogram	..	2	..	.....	Untraced; last seen 3 years ago
9 M	24	24	Paroxysmal	10	15 minutes to hours	Exertion (1) (running)	Fatigue	Electrocardiogram	6	6	30	Letter	Excellent health, active, athletic; no symptoms save an occasional paroxysm
10 M	24	24	Paroxysmal	1	12 hours	.....	Fatigue	Electrocardiogram	4	4	28	In person	Well, active, athletic; occasional premature beats from excessive smoking
11 M	24	24	Paroxysmal	1	24 hours	.....	Obesity	Electrocardiogram	..	..	..	.....	Untraced; last seen 2 years ago
12 M	25	35	Paroxysmal	Innumerable	½ hour to 2 days	Exertion (gymnastic work) alcohol (1)	.....	Electrocardiogram	6	16	41	In person	Well, active, instructor in gymnastics; paroxysm every 1 or 2 months; no other symptoms; heart normal on examination and by roentgenogram; electrocardiogram showed short PR interval with prolonged QRS interval and left axis deviation
			Paroxysmal	3	2 to 3	Alcohol and	Fatigue	Electrocardio-	6	6	35	In person	Well, active, athletic; no symptoms; heart nor-

mal on examination and by roentgenogram; electrocardiogram showed prominent P waves

13 M	29	29	Paroxysmal	3	2 to 3 hours	Alcohol and vomiting (?)	Fatigue	Electrocardiogram	6	6	35	In person	Well, active, athletic; no symptoms; heart normal on examination and by roentgenogram; electrocardiogram showed prominent P waves in leads I and II and slurred QRS waves in lead III (unchanged in 6 years)
14 M	29(?)	31	Established	1	? years	.....	.....	Electrocardiogram	6	8	37	In person	Well, active, athletic; no symptoms; heart normal on examination
15 M	29	44	Paroxysmal	2	2 to 4 days	Emotion (excitement)	.....	Electrocardiogram	2 mo.	15	44	In person	Health excellent; occasional palpitation at night; heart normal on examination
16 M	35	35	Paroxysmal	1	15 days	Alcohol and severe burns	.....	Physician	..	..	..	.....	Died of tetanus 2 weeks after being severely burned during an alcoholic debauch; necropsy showed heart to be normal
17 M	35	35	Paroxysmal	2	5 days	.....	Operation: gastro-enterostomy with ether anesthesia	Electrocardiogram	..	..	..	.....	First paroxysm on eighth postoperative day; second attack 1 month later; untraced; last seen 5 years ago
18 M	35	45	Paroxysmal	Innumerable	1 hour to 2 days	.....	.....	Electrocardiogram	9	19	54	In person	General health fairly good; paroxysms gradually increased in frequency until permanent fibrillation became established 2 years ago; slight dyspnea on effort; heart enlarged; no murmurs; by roentgenogram, T = 15.2 cm., TH = 28.7 cm., blood pressure 180/115; electrocardiogram showed auricular fibrillation, slight deviation of the axis to the left and slurred QRS complexes
19 F	35	45	Paroxysmal	Innumerable	1 to 2 hours	.....	.....	Physician	5	15	50	In person	General health fair; easily fatigued; paroxysms diminishing in frequency (three yearly); heart normal on examination and by roentgenogram and electrocardiogram
20 F	37	37	Paroxysmal	Many	Few minutes to 24 hours	Emotion (1) (excitement)	.....	Physician	13	13	50	Letter	Health excellent; occasional paroxysm of short duration
21 M	37	39	Paroxysmal	3	10 days to (?) 3 years	.....	Frequent respiratory infections; fatigue	Electrocardiogram	4	6	..	.....	Died at 48 of meningitis (tuberculous ?), 11 years after onset of paroxysms of fibrillation; no autopsy
22 F	38	50	Paroxysmal	Innumerable	10 to 12 hours	Pelvic abscess (1)	.....	Physician	2	14	..	.....	Died at 52 of acute infection (hemolytic streptococcus) involving pharynx with probable septicemia; no necropsy
23 M	39	54	Paroxysmal	Innumerable	5 to 24 hours	.....	.....	Physician	12	27	66	In person	General health fair; paroxysms occur every 2 weeks; dyspnea on effort; heart enlarged on examination and by roentgenogram, T = 14.6 cm., TH = 24.6 cm.; apical and aortic systolic murmurs; blood pressure 220/120; electrocardiogram showed moderate deviation of the axis to the left

* In this and the following table, T means transverse diameter of heart and TH, internal diameter of the thorax.

TABLE 2 (Subgroup 2).—*Data on Patients with Auricular Fibrillation of the Paroxysmal Type with no Other Evidence of Cardiac Disease (Age at Onset Over 40 Years)*

Case and Sex	Age at Onset	Age When Examined	No. of Attacks	Duration of Attacks	Probable Precipitating Cause	Possible Contributory Factors	Diagnosed by	Years Followed	Years Since Onset	Age at Present	Follow-Up	Follow-Up Data
24 M	41	41	1	Few hours	Malarial chill for treatment of syphilis of the central nervous system	.....	Electrocardiogram	1	1	42	In person	General health good except for spells of confusion; occasional premature beats; heart normal on examination and by roentgenogram; electrocardiogram showed auricular premature beats, inverted lead III (transversely placed heart)
25 M	42	42	1	Few days	.....	Fatigue	Electrocardiogram	2	2	44	Letter	General health fair; symptoms of neurocirculatory asthenia but no recurrence of auricular fibrillation
26 M	43	43	8	5 hours to 9 weeks	.....	Fatigue	Electrocardiogram	12	12	55	In person	General health fair; easily fatigued; occasional pains in legs; palpitation from premature beats and an occasional paroxysm; heart normal in size; apical systolic murmur; electrocardiogram showed auricular premature beats
27 M	43	43	2	2 days to 1 week	.....	Obesity; tobacco	Electrocardiogram	6 mo.	6 mo.	..	.....	Followed for six months; last seen six years ago; well, had lost 30 pounds; no symptoms
28 M	44	44	2	Several days	.....	.....	Physician	6	6	50	In person	General health good; obese; no symptoms; heart not enlarged; no murmurs; roentgenogram showed a transversely placed heart with T = 13.8 cm., TH = 27.2 cm.; electrocardiogram showed inverted lead III
29 M	44	44	Many	2 to 3 days	.....	Respiratory infections; tobacco (1)	Electrocardiogram	10	10	54	Letter	General health good; continued paroxysms of one or two yearly; no other symptoms; heart normal on physical examination and by roentgenogram and electrocardiogram
30 M	44	46	Many	Several hours to 1 year	.....	Nervous strain; fatigue	Electrocardiogram	..	2	46	.....	Examined for first time recently
31 M	46	46	Many	Several hours	Thyrotoxicosis	.....	Physician	8	8	54	Letter	Eight months after first observation, condition diagnosed as thyrotoxicosis; thyroidectomy performed; seven years after operation, well except for occasional paroxysms
32 F	48	48	13	1 to 2 hours	.....	Chronic bronchitis; fatigue	Physician	4	4	..	.....	Died at age of 52, suddenly, several weeks after attack of pneumonia; cause (?) coronary disease; no autopsy
33 M	48	53	5	3 hours to 2 days	.....	.....	Physician	8	13	61	Letter	General health excellent except for occasional attacks of diarrhea; no cardiac symptoms; no paroxysms for years; heart normal; electrocardiogram showed PR interval to be from 0.22 to 0.24 seconds, slight left axis deviation
34 M	49	64	6	2 to 10 hours	.....	Overeating (1)	History	2	17	66	In person	General health good; one paroxysm in past two years; no other symptoms; heart normal on physical examination and by roentgenogram and electrocardiogram
35 M	52	52	12	12 hours to 2½ days	.....	.....	History	11	11	63	In person	General health good; no paroxysm for 2½ years; no symptoms; heart full-sized, no murmurs; roentgenogram showed T = 12.7 cm., TH = 24.5 cm.; blood pressure 160/95; electrocardiogram showed ventricular premature beats, no abnormal deviation of the axis
36	52	56	Innumerable	1 hour to 2 days	.....	Nervous strain	Electrocardiogram	7	11	63	Letter	General health fair; frequent paroxysms continue; has colitis
37	52	52	1	Few hours	.....	.....	Electrocardiogram	1	1	53	Letter	General health good; nervous; no recurrence of auricu-

36 M	52	56	Innumerable	1 hour to 2 days	.....	Nervous strain	Electrocardiogram	7	11	63	Letter	General health fair; frequent paroxysms continue; has colitis
37 M	53	53	1	3 days	.....	Nervousness	Physician	8	8	61	Letter	General health good; nervous; no recurrence of auricular fibrillation; has occasional premature beats
38 M	53	58	Many	15 hours to 3 days	.....	.....	Electrocardiogram	11	16	69	In person	General health good; from two to three paroxysms yearly (17 in last seven years); chops wood; walks from 3 to 6 miles daily; no dyspnea; heart full-sized, no murmurs; blood pressure 150/80; roentgenogram showed T = 12.8 cm., TH = 24.4 cm.; aorta tortuous; electrocardiogram showed no abnormal deviation of the axis; inverted T wave in lead III
39 M	53	62	Innumerable	1 to 2 hours	.....	.....	Physician	9	17	70	Letter	General health good; paroxysms continue but fewer and less disturbing; two years ago had prostatectomy, phlebitis, and pulmonary embolism with recovery
40 M	56	56	2	2+ days	Gallbladder colic	.....	Physician	6 mo.	1	57	In person	General health fairly good; occasional pain in chest and shoulder during bad weather; no recent paroxysms; no cardiac symptoms; heart, blood pressure and roentgen evidence normal; electrocardiogram showed slight left axis deviation
41 M	57	60	2	48 hours to 3 months	.....	.....	Electrocardiogram	7	10	67	Letter	Nervous, easily fatigued, otherwise in good health; no paroxysm in past seven years
42 M	58	58	1	6 hours	Operation: partial gastrectomy with ether anesthesia	.....	Physician	..	..	..	.....	Died third postoperative day (gastric carcinoma) of peritonitis; auricular fibrillation on second day; autopsy revealed heart to be normal
43 M	58	63	Innumerable	15 minutes to 1 hour	.....	Mild arthritis	Physician	11	16	74	In person	General health good for ten years; paroxysms continue but less frequent and less disturbing; prostatic hypertrophy; heart not enlarged; harsh apical systolic murmur, blood pressure 140/85; roentgenogram of heart normal; electrocardiogram showed low T wave in lead I, prominent T wave in leads II and III
44 M	60	62	Innumerable	5 minutes to 12 hours	.....	Fatigue	History	6	8	68	In person	Health fair; frequent paroxysms (1 weekly); no other symptoms; heart not enlarged, no murmurs; roentgenogram showed T = 11.6 cm., TH = 25.4 cm.; electrocardiogram showed normal record
45 M	64	64	Many	1 to 5 hours	Alcohol (2); bronchopneumonia (2)	.....	Physician	8	8	72	Letter	Frequent paroxysms, very disturbing, with pain in left side of chest
46 M	64	65	Innumerable	Few minutes to hours	.....	Nervous strain; fatigue	Physician	5	6	70	Letter	Patient known to be living but exact status undetermined; last seen one year ago with frequent paroxysms, otherwise in good health
47 M	67	67	Many	1 hour to 4 days	.....	Overeating (1)	Physician	9	9	76	In person	Excellent health except for indigestion and occasional paroxysms; heart normal on examination and by roentgenogram and electrocardiogram; blood pressure 120/70
48 M	71	71	1	1 day	Lobar pneumonia	.....	Physician	..	..	..	.....	Auricular fibrillation appeared on third day of lobar pneumonia; died on fourth day; no autopsy
49 M	75	75	1	6 hours	.....	Acute urinary frequency and diarrhea	Physician	6	6	81	Letter	Patient known to be living, but exact status undetermined

The basal metabolic rate was normal or reduced in the 8 cases in which a test was made.

Type, Frequency and Duration.—According to type, the condition was classified as established or permanent in 3 cases, in which the arrhythmia was of several years' duration without a tendency toward spontaneous caseation, and as transient or paroxysmal in 46 cases. Reference to tables 2, 3 and 4 reveals that over half the patients had few paroxysms. Great variation in the duration of paroxysms was noted, from the shortest of a few minutes to the longest lasting one year; usually the paroxysms continued a few hours or days. The 3 patients with established fibrillation thought that the irregularity had been present since childhood; 1 at the age of 8 was found by his physician to have an irregular pulse.

Etiology.—The discoverable etiologic factors in the present group are few. As shown in tables 1 and 2, the factors have been divided into probable precipitating and possible contributory factors. In the former group are placed those factors which seemed intimately related to the onset of a paroxysm, namely, toxic (pneumonia, malarial chill, pelvic abscess, alcohol, ether), traumatic (burns) and reflex (gallbladder colic, gastric resection for carcinoma, vomiting) and those due to exertion (running, gymnastic work) and nervous strain (excitement, emotion, fear). The latter group contains less definite but possible causes, namely, fatigue, a sensitive nervous system, obesity and toxic factors such as mild infections, carbon monoxide and tobacco, in which the association was plausible but remote. In no instance when more than one paroxysm had occurred was the same etiologic factor responsible for all or even more than two paroxysms in the same person. The majority of our patients were of a nervous, "high strung" type, and a history of fatigue, mental or physical, at the time of initial or subsequent attacks was common. No conclusive etiologic relationship was found to exist between past infections or the habitual use of coffee, tea and tobacco and the occurrence of fibrillation. Undemonstrated coronary sclerosis may have been a factor in some of the older group of patients.

Follow-Up Study.—Of the entire group of 49 patients with auricular fibrillation, 21 were followed up in person, 15 were traced by letter (from physician or patient), 6 were found to be dead, 2 are known to be living but their exact status is not known, 1 patient was seen for the first time recently and 4 could not be traced. In order to bring out any existing differences in prognosis, the younger and older patients have been segregated into two subgroups, those under and those over 40 years, according to their age at onset as determined from the history. Tables 2 and 3 give the pertinent data for each subgroup, and table 3 summarizes the present status of the patients followed up in relation to frequency of paroxysms.

Subgroup 1: Onset in patients under 40 years of age (23 cases): In this subgroup, which includes all 3 patients with established fibrillation, 17 patients have been followed (11 in person) for periods of from four to thirty-three years since the onset; 3 are dead of various causes (to be discussed later), and 3 have not been traced. In 7 patients the paroxysms have ceased, 5 have occasional paroxysms now and 2 have frequent attacks. Except for 2 patients who have had definite cardiovascular changes, all may be said to have good health. One of the patients with established fibrillation has maintained normal rhythm for six years after at least two years of continuous fibrillation; all 3 of this group possess otherwise excellent health. Those patients with complications deserve brief mention. In case 18 the patient had had paroxysms of fibrillation for seventeen years, gradually increasing in frequency until two years ago when permanent

fibrillation became established; now at 54, though his health is fair, he has slight dyspnea on effort, cardiac enlargement, hypertension and moderate left axis deviation disclosed by electrocardiogram. The patient in case 23 had had innumerable paroxysms which occurred every two weeks, and in time moderate dyspnea, cardiac enlargement, apical and aortic systolic murmurs, hypertension and moderate left axis deviation have developed. Of the 3 deaths, one was possibly related to the heart. In case 22 the patient, a woman, died at the age of 52 years of acute hemolytic streptococcic pharyngitis, with probable septicemia, fourteen years after the first appearance of innumerable paroxysms of fibrillation. The auricles were fibrillating at the time of death; no postmortem examination was made. In the other 2 patients (cases 16 and 21) death was due to tetanus and meningitis, respectively, with normal cardiac findings at necropsy in the former.

TABLE 3.—*Data on the Cases of Auricular Fibrillation Showing the Relationship of the Present Status of the Patient to the Number of Paroxysms with a Comparison According to the Age at Onset*

			Present Status of the Patient										
			Paroxysms				Complications						
								Heart					
Age at Onset, Years	Number of Paroxysms	Number of Cases	Ceased	Few	Frequent	Permanent Fibrillation	Dyspnea	Murmurs	Full-sized	Definitely Enlarged	Hypertension	Prolonged P R Interval	Hyperthyroidism
Under 40	Few	9	6	3	..	..	..	..	..	..	..	..	..
	Many	1	..	1	..	..	..	..	..	..	..	..	..
	Innumerable	4	..	1	2	1	2	1	..	2	2	..	..
	Established fibrillation	3	1	..	..	2	..	..	..	..	..	..	..
Total		17	7	5	2	3	2	1		2	2		
Over 40	Few	10	8	2	..	..	1	..	1	..	1	1	..
	Many	5	..	4	1	..	..	..	1	..	1	..	1
	Innumerable	4	..	2	2	..	..	1	..	..	..	..	..
	Established fibrillation	0	..	..	..	..	..	..	..	..	..	..	..
Total		19	8	8	3		1	1	2		2	1	1

Subgroup 2: Onset at over 40 years of age (26 cases): Nineteen patients had been followed up (10 in person) for intervals ranging from one to seventeen years after onset, 3 are dead, 2 are known to be living, 1 was seen for the first time recently and 1 has not been traced. In 8 patients attacks have ceased; an equal number have occasional paroxysms, and 3 have frequent attacks. Mild cardiovascular changes have occurred in 5 patients and in 1 hyperthyroidism developed. The complications that have occurred consist of mild hypertension and "full-sized hearts" in 2 patients (cases 35 and 38), a loud apical systolic murmur without cardiac enlargement in 1 (case 43), a prolonged PR interval (from 0.22 to 0.24 second) which persisted unchanged for one year in 1 (case 33) and the development of hyperthyroidism requiring thyroidectomy in 1 (case 31) eight months after he was first observed. Of the 3 recorded deaths 1 (case 32) was probably due to cardiac disease. A woman with paroxysms of fibrillation for four years dropped dead at the age of 52 on returning to work in a factory after convalescing from pneumonia; death was ascribed to coronary disease, but autopsy was not performed. In the others (cases 42 and 48) death followed peritonitis and lobar

pneumonia, respectively; in 1 case autopsy revealed a normal heart. The exact status of 2 patients known to be living has not been determined, but 1 of these (case 46) was last seen one year before this report was written, at which time he was having frequent paroxysms, though his general health was good.

Comment: It should be emphasized that the cardiovascular complications recorded here are present only in elderly persons years after the inception of auricular fibrillation, and in each instance there is the same fundamental pathologic background, arterial sclerosis, with differences only of degree and distribution. A certain proportion of similar changes is to be expected in any group of persons observed in the late decades of life. That the same factor is responsible for the genesis of fibrillation and for the production of cardiac complications seems unlikely except perhaps in some of those in whom fibrillation appeared well after middle age at the time when arteriosclerotic changes usually appear. Improvement, manifested by cessation of paroxysms or gradual diminution in their frequency, was shown in 66 per cent of the whole group followed. A priori, one would anticipate less improvement in the older age group, but, as demonstrated in table 4, no significant differences between the two subgroups exists.

TABLE 4.—*Results of Quinidine and Digitalis Therapy in Auricular Fibrillation*

	Quinidine					Digitalis		
	Number of Patients Treated	Effective		Ineffective	Ineffective Later	Number of Patients Treated	Normal Rhythm Restored	Ineffective
Age at Onset, Years		Alone	With Digitalis					
Under 40	12	6	5	1	2	12	1	11
Over 40	20	17	..	3	3	7	2	5
Total	32	23	5	4	5	19	3	16

Prognosis.—On the basis of the experiences given here, the outlook for the patients with fibrillation but with no signs of cardiac disease appears good and conforms to that of the similar group followed by Parkinson and Campbell.[6b] In striking contrast, on the other hand, are the studies reported by Stroud, LaPlace and Reisinger[50] and Cookson[51] on persons with auricular fibrillation accompanied by cardiac disease, in whom the average duration of life was from two and a half to seven years. More than half of our group with paroxysmal fibrillation showed some degree of improvement, with little tendency toward the development of the permanent form. Cessation of paroxysms was confined entirely to those patients who had had but few attacks. As would be expected, the best prognosis is held by the younger persons, in whom paroxysms have occurred infrequently. After considerable intervals the cardiovascular changes in our group have been few, rarely serious and in some instances wholly incidental to the presence of fibrillation. Hyperthyroidism was an uncommon complication. The mortality from auricular fibrillation or from cardiac disease was almost negligible.

Treatment.—In this series of cases of auricular fibrillation, in which the majority of patients were of a nervous, emotional temperament, constant reassurance along with general measures, namely, rest, exercise, diversion and

50. Stroud, W. D.; LaPlace, L. B., and Reisinger, J. A.: The Etiology, Prognosis and Treatment of Auricular Fibrillation, Am. J. M. Sc. **183**:48, 1932.

51. Cookson, H.: The Etiology and Prognosis of Auricular Fibrillation, Quart. J. Med. **23**:309, 1930.

avoidance of fatigue, nervous strain and any factors thought to precipitate paroxysms, proved helpful. Sedative drugs were useful in the very nervous patients. Quinidine was the most effective therapeutic agent and in our opinion is the drug of choice. It was used in 32 of our 49 cases, in doses ranging from 3 to 6 grains (0.195 to 0.39 Gm.) from three to six times daily, and was effective in restoring normal rhythm or preventing paroxysms in 28. It became ineffective after prolonged use in 5 of these 28 cases, thus reducing its final efficacy to 72 per cent. The drug was slightly more effective in the younger than in the older age group. Much less effective was digitalis; normal rhythm returned in but 3 of 19 instances when it was used. Table 4 summarizes the results of drug therapy.

AURICULAR FLUTTER

The data on 7 cases of auricular flutter occurring without other manifestations of cardiac disease can be most clearly presented by means of brief summaries giving the facts of major importance in each instance.

CASE 1.—D. T., a man aged 27, a printing-press feeder, was first seen by us on June 30, 1926, with a history of innumerable attacks of cardiac disturbance for fifteen months, characterized by sudden rapid, regular palpitation, choking, dyspnea, weakness, dizziness and faintness, occurring on the slightest exertion and lasting from fifteen to twenty minutes, with abrupt cessation, leaving the patient weakened. Digitalis seemed to help, and with rest recently he had had fewer attacks. The past history revealed whooping cough, influenza followed by jaundice, rheumatism in the left foot (for one week years ago), sore throat and colds and recent loss of weight (16 pounds [7.3 Kg.] in nine months). The patient drank coffee twice daily, and although he was formerly an inveterate smoker, he now rarely used tobacco, and he took no alcohol. Physical examination revealed tuberculosis at the apex of the left lung; no enlargement of the heart; no murmurs; a rate of 150 (slowed to 100 with orbital pressure), and a blood pressure of 125 mm. of mercury systolic and 75 mm. diastolic. Laboratory examination (blood, urine, stool) showed nothing abnormal. Roentgen study of the lungs revealed bilateral apical pulmonary tuberculosis; a plate taken at 7 feet (213 cm.) showed the heart to be normal in size and shape; a dental film indicated absorption about the root of one molar. Several electrocardiograms showed auricular flutter, with the auricular rate varying from 250 to 292, and the ventricular rate from 60 to 275, with 1:1, 2:1, 3:1 and 5:1 rhythm. With 1:1 rhythm at auricular and ventricular rates of 275, intraventricular block of the left branch type appeared.

Treatment gave the following results: quinidine alone produced 3:1 block; digitalization produced from 3:1 to 5:1 block, and quinidine (6 grains six times daily for two days) restored normal rhythm, after sixteen days of flutter. The patient was placed in a sanatorium for six months and was then discharged with healed tuberculosis. On March 15, 1934, he was readmitted to the sanatorium with advanced pulmonary tuberculosis. Normal rhythm had been maintained for eight years; the patient had no cardiac symptoms; his heart was normal in size with no murmur, and his blood pressure was 110 systolic and 70 diastolic. It was nine years since the onset of auricular flutter.

CASE 2.—C. V., a woman, aged 28, a technician, first examined by us on March 29, 1923, had a history of from ten to fifteen paroxysmal attacks of cardiac disturbance beginning at the age of 16 (twelve years before). The attacks were characterized by an abrupt onset of rapid, regular palpitation, fluttering in the chest and a sensation of smothering, induced by strenuous exertion, such as playing tennis or basketball and running for a street-car; they lasted from five to ten

minutes and were relieved almost immediately by rest, after which exercise could be resumed in normal fashion. The longest paroxysm, brought on by running, lasted four hours, with spontaneous cessation. The patient's health was excellent, and she had no other symptoms of cardiac disease. The past history was entirely irrelevant except for the usual childhood diseases—measles, mumps, chickenpox and occasional tonsillitis. Tea, coffee, tobacco and alcohol were little used. Physical examination revealed nothing of importance. The heart was normal in size; there were no murmurs; the rate during a paroxysm was rapid and regular at 165 per minute, and an electrocardiogram showed auricular flutter with a 2:1 block, with the auricular rate 330 and the ventricular rate 165. During normal rhythm a normal record was obtained with a ventricular rate of 100.

For the next eleven years she enjoyed perfect health except for a carbuncle in 1925 and two or three paroxysms of tachycardia a year of from one to five minutes' duration each, similar to the duration of the proved flutter. In 1929 a basal metabolism test showed a rate of plus 4 per cent. In April 1934, at the age of 39, twenty-three years after the beginning of the attacks, the patient was perfectly healthy and played tennis and swam without cardiac embarrassment. Her heart was normal in size, rate and rhythm, with no murmurs, and the blood pressure was 125 systolic and 80 diastolic. The electrocardiogram showed normal rhythm, with a diphasic P wave in leads II and III and a flat T wave in lead III. The paroxysms have been of such short duration that no medication has been required. It was twenty-three years since the onset.

Case 3.—H. M., a salesman, aged 34, of a nervous temperament, was first seen by us on Oct. 3, 1921, with a history of premature beats for thirteen years beginning after an attack of pneumonia at the age of 21 and of innumerable attacks of rapid, usually regular, but occasionally irregular, palpitation for eight years. The attacks were accompanied by weakness, at first infrequent, but for the three years prior to examination coming every three weeks, lasting from one to three hours, and subsiding spontaneously. The paroxysm from which he sought relief had been present constantly for six weeks. No precipitating cause for the paroxysms was apparent. The past history revealed diphtheria in childhood, pneumonia, jaundice at 25, influenza at 31 and occasional sore throat. Coffee and tobacco were used in moderation. Three years before he was first observed by us he qualified for life insurance. Physical examination by us revealed little that was abnormal; the heart was not enlarged, the apex impulse being in the fifth space 7 cm. to the left of the midsternum and within the midclavicular line; there were no murmurs, the sounds were rather weak, and the rhythm was rapid and irregular; the blood pressure was 135 systolic and 90 diastolic; there was slight edema of the left leg from varicosities, but there was no evidence of congestive failure. Several electrocardiograms taken over a two week period showed auricular flutter with auricular rates from 305 to 310 and ventricular rates from 90 to 155, with changing auriculoventricular block varying from 2:1 to 5:1. On digitalis therapy little improvement was noted, but with 28 grains (2.42 Gm.) of quinidine in divided doses in one day normal rhythm was restored after eight weeks of constant flutter. The electrocardiogram made after this treatment gave normal results.

For the next five years the patient had frequent paroxysms lasting several hours, usually at night, each responding favorably to 6 grains of quinidine. The paroxysms were apparently more frequent during periods of mental stress. He was last heard of by us in July 1931, when he was admitted to a hospital with phlebitis of an extremity and pulmonary embolism. He had continued to have frequent attacks of palpitation, and slight substernal distress on exertion, not thought to be angina pectoris, had developed. Enlargement of the left ventricle

was evidenced on roentgen study, and an electrocardiogram revealed auricular fibrillation. The blood pressure was normal. An electrocardiogram made after normal rhythm had been restored with digitalis and quinidine revealed a prolonged PR interval (0.26 second) and ventricular premature beats. Since his discharge in 1931 the patient's fate has been unknown to us; efforts to follow him have been unsuccessful. The patient was followed for eighteen years after the onset.

CASE 4.—W. R., a lawyer aged 40, first seen by us on March 11, 1932, had a history of premature beats for six months, present only with a cardiac rate below 100; this was first noted by his wife (formerly an anesthetist), for the patient was unaware of them subjectively. He had had no symptoms of cardiac disease, and his exercise tolerance was normal. The past history revealed none of the common infectious diseases. For one year he had been under treatment for syphilis of the central nervous system in the early stage, and consultation for an opinion on the condition of his heart was requested during treatment with malaria. Five years previously, at 35, he passed an examination for life insurance. Tea, coffee and alcohol were used moderately, but tobacco was used in larger amounts (from four to five cigars daily). The patient's health had been excellent except for the aforementioned disturbance. Physical examination (three hours after a malarial chill) revealed a well developed and well nourished man who was clear mentally but concentrated with difficulty. The pupils were fixed to light, and slight arcus senilis was present. The heart was of normal size, with fair sounds and no murmurs. The rhythm was irregular owing to frequent premature beats, at a heart rate of 86. The blood pressure was 105 systolic and 70 diastolic. Following a malarial chill with high fever the heart rate was found to be very rapid, and an electrocardiogram taken on March 12, 1932, showed auricular flutter, an auricular rate of 300 and a ventricular rate of 140, with 2:1 and 3:1 block. After 10 grains (0.65 Gm.) of quinine was given for the malaria the flutter of several hours' duration ceased. The electrocardiogram then showed auricular and ventricular extrasystoles.

One year later (in July 1933) the patient was seen again under similar circumstances in the hospital with auricular fibrillation (detected by electrocardiogram) following combined malarial and typhoid vaccine therapy for the syphilis. In April 1934 he was in good health except for occasional symptoms of disturbance of the central nervous system (spells of confusion); he was working hard and smoking heavily. He had occasional premature beats but no cardiac symptoms. His heart was normal in size and rate, with premature beats but no murmurs. The blood pressure was 115 systolic and 75 diastolic. The electrocardiogram showed auricular premature beats and total inversion of lead III, with slight slurring of the QRS waves in lead II. Fluoroscopic examination of the heart revealed a transverse normal heart and a normal aorta. It was two years since the onset.

CASE 5.[52]—E. J., a machinist aged 49, first seen by us on July 16, 1924, had a history that two years before, while running for a street-car, rapid fluttering of the heart began, accompanied by choking sensation, dizziness, faintness and some precordial distress. Improvement followed the initial attack, but palpitation recurred on slight exertion and lasted from thirty minutes to one hour (presumably from the assumption of 1:1 rhythm). Two months after the onset the patient was forced to stop work because of the frequency of the distressing palpitation. The past history revealed measles, mumps and scarlet fever in childhood and a hemorrhoidectomy at 48. The patient had otherwise enjoyed good health

52. Case 5 was previously reported by Sprague and White.[40]

and once had been a professional baseball player. Physical examination revealed a slender man with a hydrocele. The apex impulse and left border of dulness of the heart were in the fifth space 9 cm. to the left of the midsternal line and just beyond the midclavicular line (8.5 cm.); the sounds were of good quality; there were no murmurs; the rate was from 120 to 150, and the blood pressure was from 100 to 125 mm. of mercury systolic and from 76 to 80 diastolic. Examination of the blood and urine and Wassermann tests yielded normal results. The basal metabolic rate was minus 9. Roentgenograms showed slight increase in the transverse diameter of the heart (probably due to dilatation from prolonged flutter) and slight torsion of the aorta. An electrocardiogram showed auricular flutter with 2:1 block, an auricular rate of 240 and a ventricular rate of 120. After exercise a 1:1 rhythm was noted, with both the auricular and the ventricular rate 240 and aberrant ventricular complexes (from intraventricular block). Digitalis and quinidine in large dosage failed to restore normal rhythm.

On Nov. 11, 1927, for reasons unknown, after five years of continuous flutter, normal rhythm returned spontaneously, bringing great relief to the patient. In January 1934, at the age of 59 years, twelve years after the onset and seven years after the offset of the auricular flutter, the patient enjoyed excellent health, having had no symptoms referable to his heart since the cessation of the flutter. The apex impulse and left border of dulness were 7.5 cm. to the left of the midsternum (no enlargement); there were no murmurs; the rate was 72, and the rhythm was regular. The blood pressure was 120 systolic and 75 diastolic. An electrocardiogram revealed normal rhythm with slurred S waves and flat T waves in lead III; it was essentially normal. It was twelve years since the onset.

Case 6.—W. H., a retired business man aged 54, first seen by us on March 7, 1922, had a history of attacks for fifteen years consisting of rapid heart rate, usually regular but also irregular at times, accompanied by weakness, faintness and dull precordial ache, appearing every few days and lasting from a few minutes to five or six hours, with abrupt onset and offset. There was no known provoking cause of the paroxysms. One attack had been stopped by ocular pressure. The past history revealed no serious illnesses; the patient's general health had been good. He smoked moderately. Physical examination revealed nothing of importance except tachycardia. The heart was not enlarged; the sounds were faint; there were no murmurs; the rate was about 240; the blood pressure was 115 systolic and 80 diastolic (later with normal rhythm), and there was no congestion. An electrocardiogram showed auricular flutter with 1:1 rhythm, both the auricular and ventricular rates being 255. With quinidine sulphate therapy (12 grains) normal rhythm was restored after nine hours of flutter, which at times on physical examination had given very irregular cardiac rhythm, suggesting changing degrees of block or auricular fibrillation. An electrocardiogram made during normal rhythm showed a rate of 70, with slight left axis deviation (angle: minus 15 degrees).

For the next twelve years the patient was observed at intervals. He had frequent paroxysms of mostly irregular palpitation (undoubtedly auricular fibrillation), though at times it was regular, every ten days or two weeks, lasting from ten to twenty-four hours, coming most frequently at night. The attacks were relieved by quinidine at first; later this drug proved ineffective in controlling the attacks and was voluntarily discontinued. Digitalis was ineffective also. In April 1934, at the age of 66, twenty-seven years after the first attack, the patient continued to have frequent paroxysms; his general health was fairly good though there was some dyspnea on exertion; his heart was slightly but definitely enlarged, with slight apical and aortic systolic murmurs and an accentuated aortic second

sound, and the blood pressure was 220 systolic and 120 diastolic. Orthodiagraphy showed the heart and aorta to be enlarged (transverse cardiac diameter, 14.6 cm.; internal thoracic diameter, 24.6 cm.). An electrocardiogram showed normal rhythm with moderate left axis deviation. It was twenty-seven years since the onset.

CASE 7.—G. H., a broker aged 66, was first seen in consultation by us on July 29, 1930, because of auricular flutter. He had always been strong, well and active but had been under great nervous strain for one year. Two weeks before examination a gangrenous appendix had been removed, and the area was successfully drained. On the eighth postoperative day the patient had transient sharp but not severe precordial pain, which was relieved at once by belching gas. On the ninth day a rapid irregular pulse was discovered which proved by electrocardiogram to be due to auricular flutter with an auricular rate of 320 and a ventricular rate of 100 to 120 with 2:1 and 4:1 block. Digitalization converted the rhythm to normal after four days of flutter. Prior to this paroxysm the patient had not had cardiac symptoms. Physical examination revealed nothing of importance except for the surgical wound. The heart was not enlarged; the sounds were fair in quality and rather soft; there were no murmurs; the rate and rhythm were normal, and the blood pressure was 130 systolic and 80 diastolic. The urine was normal. A second electrocardiogram, made three days after the first, showed auricular premature beats with slightly low voltage.

In December 1931 the patient was successfully operated on for fracture of the head of the femur. The heart was normal at that time. In 1934, at the age of 70, four years after the first and only paroxysm of auricular flutter, he was well except for mild arthritis; he played eighteen holes of golf, and aside from slight dyspnea on climbing hills he had no symptoms. His heart was of normal size; the sounds were good; there were no murmurs, and the blood pressure was 140 systolic and 85 diastolic. Fluoroscopic examination revealed an apparently normal heart and aorta. An electrocardiogram showed auricular premature beats, a rate of 75, no abnormal axis deviation and normal T waves.

SUMMARY

1. *Auricular Fibrillation in Patients Without Other Evidence of Cardiac Disease.*—We have presented observations on 49 patients in whom auricular fibrillation occurred without other signs of cardiac disease. The ages varied from 21 to 75 years. All save 3 cases were of the paroxysmal type; few paroxysms occurred in 46 per cent of these. Definite etiologic factors were few, but instances have been presented in which the appearance of fibrillation was related to pneumonia, malarial chill, pelvic abscess, alcohol, ether, burns, gallbladder colic, vomiting, surgical operation, exertion and emotion (excitement and fear). Follow-up studies on 90 per cent of the entire group revealed 1 probable death from cardiac disease four years after the onset of paroxysms of auricular fibrillation, 6 patients with cardiovascular complications which had appeared some years after the first auricular fibrillation and 1 patient in whom hyperthyroidism had developed. The essential data have been recorded briefly, and a comparison of the follow-up results, with respect to age at onset, has been made. The prognosis for life and

for the maintenance of adequate cardiac function is with rare exceptions excellent, and the outlook for improvement in the number of paroxysms is also good. We regard reassurance, the avoidance of exciting factors and the use of quinidine sulfate as the most useful therapeutic measures; quinidine sulfate was consistently effective in 72 per cent of the patients of the present group to whom it was given.

2. *Auricular Flutter in Patients With No Other Evidence of Cardiac Disease.*—The histories of 7 patients with auricular flutter in whom the disorder was unaccompanied by other manifestations of cardiac disease have been reported briefly. The ages ranged from 27 to 66 years: 4 patients were 40 years old or younger when first seen by us. All attacks were paroxysmal, the number of paroxysms varying from one in 3 instances to innumerable attacks in the remainder. The duration of individual paroxysms was from a few minutes to five years, but usually several hours. Electrocardiographic proof of flutter was obtained in each patient. The common symptoms were palpitation (rapid, usually regular), choking, dyspnea, dizziness, faintness, weakness and, occasionally, precordial pain. The precipitating factor was clearly exertion in 3 cases; in 1 flutter followed a therapeutic malarial chill, and in another it appeared after the removal of a gangrenous appendix with the patient under ether anesthesia. Coffee, tea, tobacco and alcohol played no apparent etiologic rôle in these cases. Six patients have been followed up for from two to twenty-seven years after the onset; five are entirely well at the time of writing, and the remaining patient (case 7), at 66, after twenty-seven years, has some dyspnea, cardiac enlargement, apical and aortic systolic murmurs and hypertension but no signs of congestive failure. The seventh patient (case 3) was last seen eighteen years after his first attack, when he had frequent paroxysms of auricular fibrillation and roentgen study showed slight enlargement of the left ventricle. Quinidine, or its isomer quinine (case 4), was used alone in 5 cases, being effective in restoring normal rhythm or preventing paroxysms in 3 and later proving ineffective in 1 of these. Digitalis restored normal rhythm in 1 of 5 cases in which it was tried. Quinidine after digitalization converted the rhythm to normal in 2 instances.

CONCLUSIONS

Paroxysms of auricular fibrillation and of auricular flutter occur not infrequently in persons with no other signs of cardiac disease.

Follow-up studies on 54 patients of the present series (47 with auricular fibrillation alone, 5 with auricular flutter alone and 2 with both) revealed after the lapse of a significant number of years a low mortality rate, little important cardiac disease and but a single instance of hyperthyroidism.

The prognosis for life and for the maintenance of adequate cardiac function is good.

The outlook for future improvement, manifested by a decrease in frequency or complete cessation of paroxysms, is frequently good.

Thus, auricular fibrillation and auricular flutter are in some persons merely exaggerated functional disorders of the heart, no more indicative of cardiac disease or of a poor prognosis than are premature beats or auricular paroxysmal tachycardia.

NOTE.—Since the preparation of this paper, an article by Friedlander and Levine [53] has appeared with a report of cases of auricular fibrillation and auricular flutter without evidence of organic cardiac disease. Through their courtesy we find that cases 15, 2 and 7 of their series are the same as cases 1, 9 and 28 of the present series of auricular fibrillation.

53. Friedlander, R. D., and Levine, S. A.: Auricular Fibrillation and Auricular Flutter Without Evidence of Organic Heart Disease, New England J. Med. **211**:624, 1934.

MENINGITIS DUE TO TYPE I PNEUMOCOCCUS

REPORT OF A CASE WITH RECOVERY DUE TO SERUM THERAPY

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Until recent years, recovery from pneumococcic meningitis was such a rare and exceptional event that the disease was generally regarded as fatal. Kolmer,[1] Schottmüller[2] and Jochman[3] reported a mortality of 100 per cent, while Lubarsch[4] and Frankel[5] estimated the mortality as 99 per cent and 98 per cent, respectively. The first report of recovery was made by Jemma[6] in 1896. By 1911, only seven cases with recovery had been reported.[7] In 1923, Hallé[8] reported one recovery following the use of antipneumococcus serum plus fixation abscess, and in the same year Netter and Césari[9] reported a recovery due to the same treatment. In their report, for the first time, the type of pneumococcus was given. In 1928, Harkavy[10] and Globus and Kasanin[11] reported single cases and made a partial survey of the literature, describing seven cases in addition to their own.[12] One of the patients recovered spontaneously;

From St. Margaret's Hospital.

1. Kolmer, J. A.: Therap. Gaz. **44**:697 (Oct.) 1920.

2. Schottmüller, quoted by Steinbrink, O.: Beitrag zur Heilbarkeit der Pneumokokken Meningitis, Therap. d. Gegenw. **71**:188, 1925.

3. Jochman, quoted by Steinbrink, O.: Beitrag zur Heilbarkeit der Pneumokokken Meningitis, Therap. d. Gegenw. **71**:188, 1925.

4. Lubarsch, quoted by Harkavy.[10]

5. Frankel, E., quoted by Harkavy.[10]

6. Jemma: Blumgarten's Jahresberichte, 1896.

7. Rolly, F.: Deutsche med. Wchnschr. **37**:774, 1911.

8. Hallé, J.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:757 (May 25) 1923.

9. Netter, A., and Césari, E.: Bull. et mém. Soc. méd. d. hôp de Paris **47**: 763 (May 25) 1923.

10. Harkavy, J.: Pneumococcus Meningitis: Recovery with Serum Therapy, J. A. M. A. **90**:597 (Feb. 25) 1928.

11. Globus, J. H., and Kasanin, J. I.: Pneumococcus (Type IV) Meningitis: Report of a Case Treated by Forced Subarachnoid Drainage, with Recovery, J. A. M. A. **90**:599 (Feb. 25) 1928.

12. (*a*) Parkinson, P. J.: A Case of Postbasal Meningitis Due to Pneumococcus Lanceolatus, Brit. J. Child Dis. **1**:112, 1904. (*b*) Culper, R. C.: Primary Cryptogenic Pneumococcus Cerebrospinal Meningitis, with a Report of Three Cases, M. Rec. **68**:815, 1905. (*c*) Cumming, J. H.: A Case of Pneumococcus Cerebrospinal Meningitis, Lancet **2**:1924, 1912. (*d*) Rosenow, G.: Heilung der Pneumokokken Meningitis durch Optochin, Deutsche med. Wchnschr. **46**:9 (Jan. 1) 1920. (*e*) Campbell, J.: Pneumococcus Meningitis, Lancet **1**:54, 1925. (*f*)

(Footnote continued on next page)

in the others recovery followed treatment with subarachnoid drainage, pneumococcus serum, pneumococcus vaccine or ethylhydrocupreine hydrochloride. In none of these cases was the type of pneumococcus specified. In Harkavy's case the condition was due to type I pneumococcus, and in Globus and Kasanin's case it was due to type IV pneumococcus. From the literature I have been able to gather reports of only eight cases of pneumococcic meningitis of specified types in which recovery has taken place.[13] To this group I wish to add a case of meningitis due to the type I pneumococcus following a fracture of the skull, in which recovery followed the intravenous and subarachnoid injection of large quantities of Felton's antipneumococcus serum of types I and II.

REPORT OF A CASE

History.—A. W., a man aged 28, was admitted to St. Margaret's Hospital on Dec. 23, 1932, after an automobile accident in which he received an extensive laceration of the occipital region of the scalp with an inverted U-shaped fracture of the occipital region of the skull. When he entered the hospital, he seemed fully conscious except for loss of memory of the events of the night of the accident. Through the wound the fracture of the occipital region was easily palpated and was examined carefully for leakage of cerebrospinal fluid, but there was none. There were a small amount of bleeding from the nose and a hemorrhage into the left ear drum. Roentgen examination revealed the fracture in the occipital region but showed no fracture at the base of the skull. The scalp wound was sutured, with drainage, and the patient was given the usual dose of tetanus antitoxin.

Course.—The drain was removed on the second day after the accident, and the occipital wound was watched carefully for leakage of the spinal fluid, but it remained dry throughout and healed by first intention. Four days after the accident the bleeding from the nose stopped and was followed by a continuous dripping of spinal fluid. Every effort was made to prevent the patient from blowing his nose for fear of forcing bacteria into the cranial cavity, but on the sixth day, being in a state of mental confusion, he blew his nose and at once complained of a generalized intense headache. Within a few hours his temperature had risen to 103 F.; his neck was stiff, and the white cell count was 40,000, with 95 per cent polymorphonuclears. A lumbar puncture yielded cloudy spinal fluid with 100 per cent of the cells polymorphonuclears but with no bacteria. A diagnosis of men-

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Ratnoff, H. L., and Litvak, A. M.: Pneumococcus Meningitis Treated with Morgenroth's Optochin Hydrochloride, Arch. Pediat. **43**:466 (July) 1926. (*g*) Brown, A. C.: Pneumococcal Meningitis with Recovery, Lancet **2**:519 (Sept. 16) 1916. (*h*) Ervin, C. E.: Pneumococcus Cerebrospinal Meningitis with Recovery, Atlantic M. J. **28**:590 (June) 1925.

13. (*a*) Bedell, C. C.: Pneumococcic Meningitis: Report of a Case with Recovery Following Cisternal Drainage, J. A. M. A. **102**:820 (March 17) 1934. (*b*) Reveno, W. S., and McLaughlin, N.: Pneumococcus Meningitis: Recovery with Felton's Serum, Ann. Int. Med. **7**:1026 (Feb.) 1934. (*c*) Synge, V. M.: Pneumococcal Meningitis, Lancet **1**:761 (April 10) 1926. (*d*) Weinberg, M. H.: Case of Pneumococcus (Type III) Meningitis Treated with Potassium Permanganate—Recovery; Plea for Its Trial, J. Nerv & Ment. Dis. **74**:38 (July) 1931. Netter.[9] Ratnoff.[12f] Harkavy.[10] Globus and Kasanin.[11]

ingitis was made, and two days later, when the lumbar puncture was repeated, pneumococci were found. Without waiting for the determination of the type of the organism, treatment was started at once, using Felton's concentrated antipneumococcus serum of types I and II. Table 1 shows the plan of treatment that was followed.

After the first intravenous injection of serum, there was a chill followed by a rise in temperature to 105 F. The temperature was irregular, ranging between 97 and 103.6 F., until the ninth day after treatment was begun; then there began a gradual fall, which continued until the thirteenth day, when the temperature reached normal. For the succeeding week the temperature was subnormal. With the onset of meningitis the pulse became slow, the rate varying between 56 and 66, and at times it was weak and irregular. The blood pressure, which had been normal between the time of the accident and the onset of the meningitis, rose to 175 systolic and 107 diastolic on the fifth day of the infection and had dropped to

TABLE 1.—*Summary of Treatment Followed*

Day of Treatment	Serum Administered Intravenously, Units	Serum Administered Intraspinally, Units	0.5% Acriflavine Hydrochloride, Cc.
1	10,000		
	10,000		
	10,000		
2	20,000	10,000	20
	20,000		40
	20,000		
3	15,000	10,000	30
	15,000	10,000	
4	30,000	10,000	
5	20,000	10,000	
6	.....	.....	
7	10,000		
Total	180,000	50,000	90

140 systolic and 95 diastolic on the fourteenth day. The white cell count, which had been 11,000 with 74 per cent polymorphonuclears two days before the onset of meningitis, rose to 40,000 with 96 per cent polymorphonuclears when the meningitis began and dropped gradually until the fifteenth day when it reached 15,000 with 76 per cent polymorphonuclears.

On the day on which treatment was begun, the spinal fluid was cloudy, with 100 per cent of the cells polymorphonuclears and with pneumococci in the smear. With each intraspinal injection, 10 to 20 cc. of spinal fluid was removed. By the fourth day of treatment the pressure had become normal and bacteria rare. By the fifth day the bacteria found in the smear were gram-negative, though similar in morphology to the pneumococcus. They were interpreted as being degenerated organisms. The culture at that time was sterile.

The organism isolated in the spinal fluid was a gram-positive, lancet-shaped, encapsulated diplococcus, which grew slowly on ascitic dextrose broth. It was soluble in bile and became agglutinated in type I pneumococcus serum, and after being dissolved in bile it could be precipitated from solution by type I pneumococcus serum.

Neurologic Symptoms.—After the accident the patient remained drowsy, being irrational at times and unable to recall the events following the accident. His mental condition improved gradually until the onset of meningitis, when he was stuporous most of the time but maniacal for short intervals and cried with the severity of the pain in his head. The neck became rigid and remained so for a week, after which it gradually relaxed. For about two weeks he remained incontinent of urine and feces. The pupils became widely dilated and ceased to react to light. On the fifth day of infection the knee jerk was absent on the left, but there was no other disturbance in reflexes and no paralysis throughout the illness. By the fifth day of treatment the Kernig sign could not be elicited, and he was rational for brief periods during the day. On the twentieth day after treatment was begun, he was rational the greater part of the time; he was able to walk on the twenty-fourth day and appeared mentally normal on the twenty-sixth day.

Recovery.—Following the illness he made a complete recovery except for ocular and certain mental disturbances. The pupils remained dilated and fixed, reacting only slightly to brilliant light but normally to accommodation. Both optic disks were hazy, with slight pallor of the right disk and choroidal pigmentation on the temporal side of the disk. There was a loss of vision in the lower half of the visual field on the right side, and a concentric contraction of the field of vision on the left. In the right eye vision was 20/200, which was corrected with lenses to 20/50; with the left eye the patient could count fingers at 6 feet (1.8 meters), and with correction vision was 20/30.

Since his recovery from his illness the patient shows no change in personality, with the possible exception of a decrease in stability and reliability. He had always used alcoholic beverages in moderately large quantities, and he imbibes more freely now than before. He has been unable to stick at a job very long because of his free use of alcohol, which may or may not be a result of his injury and infection.

It was suggested by certain of my colleagues at the time of his recovery from the infection that late complications, such as abscess or recurrence of the infection, should be expected. For this reason the patient has been observed for two years, but no recurrence of symptoms has been noted.

COMMENT

The patients who have recovered from pneumococcic meningitis varied in age from 17 months [14] to 57 years, but most of them were vigorous young adults. The sexes were almost equally affected, with a slight preponderance of men.

Source of the Infection.—Pneumococcic meningitis may follow pneumonia, infection of the upper respiratory tract, otitis media, mastoiditis, abortion [12d] or a fracture of the skull involving the sinuses or the cribriform plate. I have observed one case, with fatal termination, in which the infection took place through a wound of the scalp due to a kick by a mule which caused a depressed fracture of the skull and laceration of the dura.

14. Amesse, J. W.: Pneumococcic Meningitis: Report of Case with Recovery, Colorado Med. **28**:361 (Aug.) 1931.

Type of Organism.—Bauer and St. Clair [15] have studied the type of pneumococci found in the spinal fluid with reference to the source of the infection. Combination of their figures with those from the nine cases in which recovery was reported gives a fair idea of the relation between the source of infection and the type of organism.

Mode of Onset.—The onset of the disease is rapid and at times sudden, accompanied by mild or severe headache, rigidity of the neck and a rise in temperature to from 102 to 106 F., occasionally accompanied by chills. Vomiting is frequently encountered at the onset and may be violent and projectile. There may be drowsiness, stupor or coma, with periods of delirium. Convulsions are rare. Incontinence of urine and feces may occur. As the disease progresses, the neck becomes more rigid and at times is retracted, and there may be slight opisthotonos. The Kernig sign is generally present. There may be photophobia. The pupils may be contracted or dilated widely. The

TABLE 2.—*Type of Pneumococcus and Source of Infection in Twenty-One Cases of Pneumococcic Meningitis*

Source of Infection	Type I	Type II	Type III	Type IV
Otitis media	..	..	4	1
Sinusitis	3	..	..	3
Fractured skull	2	..	..	2
Pneumonia, late	..	..	1	..
Source obscure	1	..	..	3
Infection of upper respiratory tract	1	..	..	..

fundus is generally congested, and there may be optic neuritis. Paralysis of the external or of the internal rectus muscles is sometimes encountered. Reaction of the pupils to light is usually present but sluggish. The knee jerks are generally diminished or absent but are occasionally hyperactive. A Babinski sign is rarely found.

Pulse.—The pulse is frequently relatively slow. Bedell's patient [13a] had a pulse rate of 94 with a temperature of 106 F.; Clark's patient [16] had a pulse rate of 64, and my patient at the onset had a pulse rate varying between 56 and 66. Less frequently the pulse is rapid. An elevation in blood pressure has been rarely reported, though in my case it reached 175 systolic and 105 diastolic.

The white cell count is always elevated, with an increase in the percentage of polymorphonuclears, the average count being around 25,000 with 85 per cent polymorphonuclears.

15. Bauer, J. T., and St. Clair, H.: Pneumococcus Types in Acute Mastoiditis and "Primary" Pneumococcus Meningitis, J. A. M. A. **90**:1429 (May 5) 1928.

16. Clark, J. G.: Recovery from Pneumococcal Meningitis, Lancet **2**:1330 (Dec. 17) 1932.

Treatment.—Spontaneous recovery without any treatment has been reported by Parkinson.[12a] Weinberg [12d] reported a case of meningitis due to the type III pneumococcus in which recovery followed the rectal instillation of dilute potassium permanganate solution. Stoessinger [17] reported a recovery following the intravenous and intraspinal injection of mercurochrome. Brown [12g] treated his patient with pneumococcus vaccine. While single recoveries following the aforementioned methods of treatment are reported, the largest number of recoveries have resulted from one or more of the following methods of treatment: subarachnoid drainage, administration of concentrated antipneumococcus serum and administration of ethylhydrocupreine hydrochloride.

Subarachnoid drainage through lumbar puncture without other therapeutic measures has been used successfully by Culper,[12b] Clark [16] and Uhr.[18] Drainage by the cisternal route may become necessary owing to the fact that adhesions form at the site of the puncture and prevent drainage from the spine. Concentrated antipneumococcus serum of the Huntoon or Felton type has been given intramuscularly, intravenously, intraspinally and even into the cisterna magna. Almost invariably this method of treatment is combined with subarachnoid drainage of some form. Rosenow [12d] and Ratnoff and Litvak [12f] have reported recoveries following treatment with ethylhydrocupreine hydrochloride, and in the opinion of the latter authors, small doses of this drug markedly increase the efficacy of the antipneumococcus serum. Kolmer has stressed the advantage of the intracarotid method of injection and has outlined beautifully the details of treatment. He also discussed the use of acriflavine base and Pregl's solution. Shuller [19] has also summarized the methods of treatment, in an article reviewing the literature.

It seems from a study of the small number of cases available that the ideal method of treatment of meningitis due to type I or type II pneumococci consists of adequate doses of pneumococcus serum combined with a small amount of ethylhydrocupreine hydrochloride injected into the subarachnoid space and into a superficial vein or the carotid artery plus adequate subarachnoid drainage by lumbar puncture as long as it is feasible and by cisternal puncture if adhesions prevent drainage by the former method.[20] It is essential that the amount of serum be

17. Stoessinger, H. N.: Recovery from Pneumococcus Meningitis, Brit. J. Child. Dis. **27**:35 (Jan.-March) 1930.

18. Uhr, J. S.: Pneumococcus Meningitis: Report of Case in New-Born Infant, with Recovery, Arch. Pediat. **46**:121 (Feb.) 1929.

19. Shuller, E. H.: Pneumococcic Meningitis: Case Reports with One Recovery, J. Oklahoma M. A. **25**:137 (April) 1932.

20. Kolmer, J. A.: Newer Methods for the Prophylaxis and Treatment of Meningitis with Special Reference to Streptococcus and Pneumococcus Meningitis, Laryngoscope **42**:12 (Jan.) 1932.

ample. Harkavy's patient received 95 cc. of Felton's antipneumococcus serum intravenously, 65 cc. intraspinally and 30 cc. into the cisterna magna. Raveno and McLaughlin gave 90,000 units intravenously, 10,000 units intraspinally and 20,000 units into the cisterna magna. My patient received 180,000 units intravenously and 50,000 units intraspinally.

The chances of successful specific therapy in cases of meningitis type III or group IV pneumococci seem much less than in cases in which the condition is due to organisms of type I or II. In these cases adequate subarachnoid drainage plus the intracarotid injection of ethylhydrocupreine hydrochloride, acriflavine base and Pregl's solution is probably the best method of treatment available. Surgical cleansing of an infected mastoid or sinus is obviously essential.

CONCLUSION

Another case of recovery from pneumococcic meningitis is added to the small but ever increasing list in the literature. The organism, a type I pneumococcus, gained entrance to the central nervous system through a fissure in the cribriform plate. The patient received the largest amount of pneumococcus serum yet recorded and recovered with residual symptoms in the eyes only. Sterility of the spinal fluid was obtained five days after the beginning of treatment. Follow-up over a period of two years has revealed no recurrence of symptoms due to the infection.

NEW FORMULAS FOR PREDICTING BASAL METABOLIC RATE FROM PULSE RATE AND PULSE PRESSURE

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In their classic descriptions of thyrotoxicosis a century ago, Graves and Basedow each recorded tachycardia as a major manifestation of the syndrome. Eighty years later, when clinical calorimetry became established as a laboratory aid in the diagnosis of exophthalmic goiter, it was discovered that a relationship existed between the pulse rate and the metabolism. Benedict commented on this parallelism in his early reports, and in 1920 Sturgis and Tompkins [1] published a study of the correlation between the pulse rate and the basal metabolism in cases of hyperthyroidism. That this relationship is not peculiar to thyroid disease but is associated with the consumption of oxygen was shown by Minot and Means.[2] These workers studied the basal metabolic rate and pulse rate in a series of patients with leukemia and in a series of patients with thyrotoxicosis, and demonstrated that in both conditions the pulse rate varied with the consumption of oxygen. The persistent parallelism between the pulse rate and the metabolism led Benedict [3] to say:

> The intimate relationship between the mechanism of the circulatory system and the total metabolism has been frequently pointed out in publications from the Nutrition Laboratory. The heart rate is, with the same individual, a remarkably significant index of the total metabolism. When it is considered that the CO_2 production is directly proportional to muscular activity and heat production, and furthermore, that the blood must carry away the CO_2 and supply fresh oxygen to the tissues, in proportion to the need therefor, it is not surprising that the work of the heart bears a general relationship to the total metabolism. If the systolic discharge from the heart were uniform under all conditions one could predict that the pulse rate would be proportional to the total metabolism. Such a pro-

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1. Sturgis, C. C., and Tompkins, E. H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch. Int. Med. **26**:467 (Oct.) 1920.

2. Minot, G. R., and Means, J. H.: The Metabolism-Pulse Rates in Exophthalmic Goiter and in Leukemia, Arch. Int. Med. **33**:576 (May) 1924.

3. Benedict, F. G.; Miles, W. R.; Roth, P., and Smith, H. M.: Publication 280, Carnegie Institution of Washington, 1919.

portionality of relationship, however, is by no means established or to be inferred from experimental evidence thus far obtained.

Since the foregoing statement was written, the relationship between the total metabolism and the flow of blood has been the object of many investigations. Clinical studies of the pulse rate and the blood pressure have revealed a fairly constant parallelism between the consumption of oxygen and these two indicators of circulatory activity. More exact laboratory studies utilizing the several methods subsequently developed for measuring the flow of blood in man have added experimental evidence which indicates that the flow varies directly with the consumption of oxygen. After the degree of relationship between these variable functions of the body was established, it became possible to estimate metabolism from circulatory activity.

PREVIOUS METHODS OF DERIVING PREDICTION FORMULAS

By utilizing measurements of the parallel functions of the consumption of oxygen and circulatory activity, one of us [4] in 1922 published a formula for predicting the basal metabolic rate from the pulse rate and pulse pressure. An improved formula derived from a larger series of observations was reported in 1924.[5] The Gales [6] in England endeavored to improve and simplify the formula and in 1931 suggested the equation B.M.R. = P.R. + P.P. — 111. The following year Jenkins [7] published prediction tables, constructed from separate formulas for males and females, derived from his own data.

To what extent the various formulas have been utilized it is impossible to estimate, although various reports in the past decade indicate that they have found a place in clinical medicine. Within the last two years twenty reports [8] have emanated from workers in Europe and the

4. Read, J. M.: Correlation of Basal Metabolic Rate with Pulse Rate and Pulse Pressure, J. A. M. A. **78**:1887 (June 17) 1922.

5. Read, J. M.: Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in the Basal Metabolic Rate, Arch. Int. Med. **34**:553 (Oct.) 1924.

6. Gale, A. M., and Gale, C. H.: Estimation of the Basal Metabolic Rate, Lancet **1**:1287 (June 13) 1931.

7. Jenkins, R. L.: Basal Metabolism: II. The Basal Pulse Complex, Arch. Int. Med. **49**:188 (Feb.) 1932.

8. Umber, F.: Deutsche med. Wchnschr. **58**:1279 (Aug. 12) 1932. Habs, H.: ibid. **59**:333 (March 3) 1933. Bertheau, H.: München. med. Wchnschr. **80**:453, 1933. Hartleben: ibid. **80**:1013, 1933. Kemény, E.: Wien. klin. Wchnschr. **46**:617, 1933. Bernhardt, H.: Med. Welt **7**:581, 1933. Rosenberg, M.: ibid. **7**:184, 1933. Olmes, H.: Klin. Wchnschr. **12**:1252 (Aug. 12) 1933. Boger, A., and Voit, K.: ibid. **12**:1642 (Oct. 21) 1933. Neumann, H.: ibid. **12**: 1444 (Sept. 16) 1933. Kemény, E.: Orvosi hetil. **76**: 653 (July 23) 1932. Hank, S.: ibid. **77**:590 (July 8) 1933. Balázsy, D.: Deutsche med. Wchnschr.

(Footnote continued on next page)

United States discussing the clinical value of prediction formulas. If such formulas are to be utilized extensively it is desirable to obtain the best one possible and to ascertain definitely its degree of accuracy. With this in mind the whole subject was reinvestigated.

In all the previous formulas the equation was obtained empirically by fitting a straight line to the data. Moreover, in each instance, the pulse rate and pulse pressure have been combined by addition. This is mathematically unsound, because pulse rate and pulse pressure cannot be expressed in the same units. Even though a line is obtained which seems to fit the data, it cannot be concluded that the equation of that line represents the true relationship between the variables studied.

In dealing with biologic data, several different types of curves can often be fitted to the observations with equally close agreement. In such cases another method of attack is more satisfactory. This method consists in the theoretical deduction of a definite type of equation. Each step in the process must be based on a fact or on a reasonable assumption. Then by the calculation of constants, an attempt is made to fit the data to the equation. By this method the discovery of a true biologic relationship can more reasonably be expected. This, therefore, is the method we have employed in reinvestigating the relationship between the consumption of oxygen and the pulse rate and pulse pressure.

DERIVATION OF THE FORMULA

The formula was derived by the following steps:

I. The total production of heat is proportional to the amount of oxygen consumed during the same period. This relationship is also assumed when metabolism is measured by indirect calorimetry and requires no further discussion.

II. The consumption of oxygen is proportional to the blood flow. This is a justifiable assumption because it has been shown that (1) the blood flow (minute volume) is increased in proportion to the oxygen consumed [9] and (2) the coefficient of utilization of oxygen is not changed in cases of thyrotoxicosis,[10] even when large volumes of oxygen are consumed.

59:1433, 1933. Olmes, H.: Arch. d. méd., cir. y especialid. **36**:645 (June 10) 1933. Schor, D.: România med. **11**:229, 1933. Balázsy, D.: Aerztl. Nachrichten, no. 16, 1933. Habs, H.: München. med. Wchnschr. **80**:1260, 1933. Fine, A.: M. J. & Rec. **138**:221, 1933. Herzfeld, E., and Frieder, A.: Arch. f. Verdauungskr. **55**:199, 1934. Rachman, V. J.: Acta med. Scandinav. **83**:95, 1934.

9. Grollman, A.: The Cardiac Output of Man in Health and Disease, Springfield, Ill., Charles C. Thomas, Publisher, 1932, p. 234.

10. Davies, H. W.; Meakins, Jonathan, and Sands, J.: The Blood Gases and Circulation Rate in Hyperthyroidism, Heart **11**:299, 1925.

The truth of equations (I) and (II) is supported by 102 observations on the blood flow in cases of thyroid disease. The term reference data will be used to distinguish these observations from our own. The data are from three reports, by (1) Davies, Meakins and Sands,[10] who worked in England and used the carbon dioxide-oxygen tension method of measuring blood flow; (2) Liljestrand and Stenström,[11] who worked in Sweden, and (3) Fullerton and Harrop,[12] in this country, both of whom used the method employing nitrous oxide.

By combining the first two steps the total production of heat is found to be proportional to the flow of blood. This is confirmed in

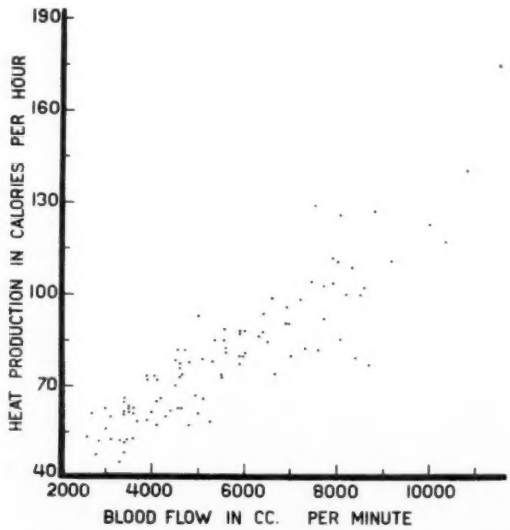

Chart 1.—The relationship between the production of heat and the blood flow.

chart 1, made from the reference data, which clearly indicates that the relationship holds over a wide range. The scatter may be entirely explained by the inaccuracies in the measurement of oxygen consumption and blood flow. The chart and the correlation coefficient, which is 0.9, suggest that a true proportionality exists between these variables.

III. Blood flow is equal to pulse rate times stroke volume. The pulse rate can be determined easily, and the problem is to find a clinical

11. Liljestrand, G., and Stenström, N.: Blood Flow and Blood Pressure in Exophthalmic Goiter, Acta med. Scandinav. **63**:99, 1925.

12. Fullerton, C. W., and Harrop, G. A.: Cardiac Output in Hyperthyroidism, Bull. Johns Hopkins Hosp. **46**:203, 1930.

measure of the stroke volume. In a given individual, stroke volume is approximately proportional to pulse pressure. This does not hold in persons of various sizes, since a large heart pumps more blood per stroke at the same pulse pressure than does a small one. Some factor of size must therefore be introduced before stroke volume can be expressed in terms of pulse pressure. The surface area of the body seems to be the most satisfactory measure for this purpose. When this factor is introduced one has:

IV. Stroke volume is proportional to the pulse pressure times the surface area.

The procedure thus far may be summarized in the following equations: (K indicates a constant which has a different value in each equation.)

(I) Total heat production = K × oxygen consumed.

(II) Oxygen consumed = K × blood flow.

Therefore, (IIa) Total heat production = K × blood flow.

(III) Blood flow = P.R. × stroke volume.

(IV) Stroke volume = K × P.R. × S.A.

Therefore, (V) Blood flow = K × P.R. × P.P. × S.A.

Equation V is supported by chart 2, founded on the reference data. This chart indicates that equation V approximates the truth, although there is somewhat more scatter than in chart 1. Then, by the substitution of equation IIa in equation V the result is:

(VI) Total heat production = K × P.R. × P.P. × S.A.

The final step in the derivation of the formula consists in dividing each side of equation VI by the surface area. This gives:

(VII) $\frac{\text{Heat production}}{\text{Surface area}} = K \times \text{P.R.} \times \text{P.P.}$

Or: Calories per square meter per hour = K × P.R. × P.P.

The use of the product of pulse rate and pulse pressure in the foregoing equations is further justified by the work of Murlin and Greer,[13] who concluded from their studies on the relation of heart action to the respiratory metabolism:

> Experiments on the human subject, in which respiratory metabolism and the heart action were determined simultaneously while the subject was resting and while doing a moderate amount of muscular work show that the product of pulse pressure (Erlanger[14]) by the pulse rate is a slightly better index of the oxygen absorption than the heart rate alone.

13. Murlin, J. R., and Greer, J. R.: The Relation of Heart Action to the Respiratory Metabolism, Am. J. Physiol. **33**:253, 1914.

14. Erlanger, J., and Hooker, D. R.: An Experimental Study of Blood Pressure and Pulse Pressure in Man, Johns Hopkins Hosp. Rep. **12**:145, 1904.

Variations in the blood flow caused by exercise, fever, ingestion of food, or anemia, which may not be accompanied by proportional changes in the consumption of oxygen, do not complicate the problem discussed here. Di-nitrophenol and its related compounds, which are known to increase metabolism without altering the pulse rate, should not complicate the problem, although their strange action calls for a solution. The only problem under consideration here is the relation of oxygen consumption to blood flow under strictly basal conditions, wherein the parallel deviations in oxygen consumption and blood flow usually result from disturbed thyroid or other endocrine function.

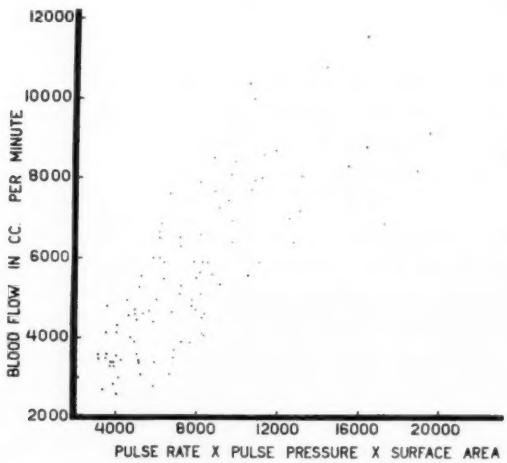

Chart 2.—The relationship between the blood flow and the product of pulse rate, pulse pressure and surface area.

THE DATA

After obtaining equation VII it was necessary to determine whether such an equation would be supported by actual observations. We proceeded to do this by gathering new data for the calculation of constants. These data (276 observations) were obtained in the departments of clinical calorimetry at the Stanford University Hospitals and St. Luke's Hospital, augmented by observations from private practice.

Extreme care was exercised in obtaining as accurate a measure of the blood pressure as possible. Several readings of the pressure were made while the patient was resting, either between the two test periods or at the end of the examination. The systolic pressure was determined

by auscultation and was checked by palpation and by observation of the changes in the amplitude of movement of the column of mercury. Auscultatory reading of the diastolic pressure was also checked by the motion of the mercury or the needle. Observations were continued until at least three successive checks were obtained. The pulse rate was recorded at frequent intervals during the test, and the lowest rates were averaged.

Since the large pulse pressure in cases of hypertension may not indicate an increased flow of blood, we considered it advisable to reject observations in which the diastolic pressure exceeded 90 mm. of mercury. Because of the difficulty in obtaining accurate measurements, children under 15 years were omitted from the series. No other exclusions were made except of the occasional patient, usually with a cardiac irregularity, in whom an accurate measurement of the pulse rate or the blood pressure was impossible.

The product of the pulse rate and the pulse pressure was correlated with the number of calories per square meter per hour, and the constants of the equations were calculated in the usual way. Separate correlation tables were prepared for the two sexes, since women have, as a rule, a faster heart rate than men, yet the normal consumption of oxygen per unit of surface area of the former is less.

The formulas derived predict the number of calories per square meter per hour rather than the metabolic rate, as previous formulas have done. Any formula that gives the metabolic rate directly must do so by disregarding the normal standards. Since these vary from 33 calories per square meter per hour in old women to 46 calories in young men, a large error may thus be introduced. This error is of little importance in persons between the ages of 20 and 45, but it is considerable outside this range. There is no more reason for discarding the standards in a prediction formula than there is for doing so in the calculation of the basal metabolism by indirect calorimetry.

To our own observations we added those of the reference series and 104 reported from the Mayo Clinic,[15] which were suitable for this purpose. We augmented our data in order to obtain observations on patients with a very large and a very small consumption of oxygen and to eliminate the personal equation by including data of several observers. From these data the following formulas were derived:

For women: Calories per square meter per hour $= 0.0047 \times \text{P.P.} \times \text{P.R.} + 23$

For men: Calories per square meter per hour $= 0.0055 \times \text{P.P.} \times \text{P.R.} + 24$

15. Sandiford, I.: Am. J. Physiol. **51**:407, 1920. Snell, A. M.; Ford, F., and Rowntree, L. G.: Studies in Basal Metabolism, J. A. M. A. **75**:515 (Aug. 21) 1920. Boothby, W. M.: M. Clin. North America **3**:603 (Nov.) 1919. Bowen, B. D., and Boothby, W. M.: J. Urol. **1**:469, 1917.

ACCURACY OF PREDICTION FORMULAS

After the formulas were obtained the basal metabolic rate was calculated on each of our 276 cases, and the rate obtained was compared with that determined by indirect calorimetry. The disparity between the sets of values is shown in table 1. For comparison we show the results obtained with the formulas of Read,[5] the Gales [6] and Jenkins [7] on the same data. As a further test, we applied all four formulas to the reference data as well as to the observations from the Mayo clinic.[15]

A similar comparison of the accuracy of four prediction formulas [16] has been made by Rabinowitch,[17] who used 200 observations made in the Montreal General Hospital and 150 reported by Davies and Eason.[18] Examination of all the comparative studies shows that Jenkins' [7] formula gives good results when the rate is low but fails to predict the higher rates. The reverse is true for the Gales' formula.

Although the new formulas appear to possess greater prediction value over the entire range than any yet published, still one calculated rate of every three will differ by more than 10 per cent from the metabolism as determined by indirect calorimetry, and not infrequently even more misleading results are obtained. It is chiefly because of these occasional large discrepancies that the value of prediction formulas has been questioned.

However, before evaluating the results of the formulas, one must ascertain the greatest degree of accuracy which can be achieved. Presumably this should be perfect agreement with the metabolic rate in all cases. It is known, however, that the basal metabolism as determined by indirect calorimetry is not entirely accurate, and, unless it were, exact agreement could not be obtained. It is obviously impossible to obtain a degree of accuracy with any formula which surpasses the accuracy of the metabolism test itself. Consequently, one must first determine the reliability of clinical calorimetry as it is performed as a routine procedure.

The question of the reliability of indirect calorimetry first arose when this clinical method was introduced as a substitute for the complicated procedure of direct calorimetry. The latter has an error of from 0.5 to 1.2 per cent [19] in its measurement of the production of

16. Read, J. M., and Barnett, C. W.: New Formulae for Prediction of Basal Metabolism from Pulse Rates and Pulse Pressure, Proc. Soc. Exper. Biol. & Med. **31**:723, 1934. Read.[4, 5] Jenkins.[7]

17. Rabinowitch, I. M.: Prediction of Basal Metabolism from Pulse Pressure and Pulse Rate, Canad. M. A. J. **32**:135 (Feb.) 1935.

18. Davies, H. W., and Eason, J.: The Relation Between the Basal Metabolic Rate and the Pulse Pressure in Conditions of Disturbed Thyroid Function, Quart. J. Med. **18**:36, 1924.

19. Sonderstrom, G. F.; Meyer, A. L., and DuBois, E. F.: Clinical Calorimetry: XI., Arch. Int. Med. **17**:872 (June) 1916.

TABLE 1.—*Accuracy of Various Prediction Formulas Compared with That of Determinations by Indirect Colorimetry* *

Data			Error Less Than														Error Over 25%			
			5%				10%				15%				20%				25%			
Source	No. of Observations	B.M.R. Range, Percentage	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B	R	G	J	R-B
Read and Barnett	276	−30 to + 73	39	36	38	45	64	62	66	73	82	77	79	88	88	83	88	93	94	88	91	98	6	12	9	2
Reference data	102	−23 to +105	29	31	15	30	55	56	30	49	70	70	39	61	80	79	50	64	85	87	57	75	15	13	43	25
Mayo Clinic	104	−40 to +103	24	19	25	30	46	42	44	49	62	67	57	69	77	78	70	82	84	89	77	88	16	11	23	12
Mean	482	−40 to +105	33	31	30	38	58	56	59	63	77	73	67	78	83	81	76	84	90	88	81	90	10	12	19	10

* The comparative prediction values of four formulas are shown: R stands for Read (1924); G for Gale; J for Jenkins, and R-B for the new formulas presented in this paper. The average deviation was as follows: Read, 9.3 per cent; Gale, 10.3 per cent; Jenkins, 10 per cent, and Read-Barnett, 8.2 per cent.

heat, the magnitude of error decreasing as the test period is lengthened. Gephart and DuBois,[20] in a series of thirty periods of one hour each, with a normal subject, noted that the results of the two methods agreed within 5 per cent in 70 per cent and within 10 per cent in 90 per cent of the periods. This careful comparison of direct with indirect calorimetry by experienced workers, however, furnishes no measure of the average error of basal metabolism as it is ordinarily determined.

In nearly every laboratory for the study of metabolism two observation periods are recorded for each patient. The agreement between the tracings made for the same patient should gage the accuracy of the method, and from a large number of tracings a close estimate of the distribution of errors in the determination of metabolism can be obtained. We accordingly collected 530 records from five different laboratories. Each was a record of at least two, and sometimes three, separate periods of observation. The metabolic rates were calculated from the curves, and the agreement between the high and the low values on each tracing were noted. When the disagreement is large, it is a widespread practice to consider the test unsatisfactory and to discard it. All such tests must, however, be included if one is to give a true idea of the reliability of the method. In a laboratory where unsatisfactory tracings are discarded a closer agreement than we are reporting would obviously be obtained on reviewing the records, but this would indicate a greater accuracy in indirect calorimetry than really exists.

The error in estimating basal metabolism has been studied by Wishart [21] and Jenkins.[22] The latter reported that the mean difference between the lower and the higher of two rates taken in succession during the same period was 4.7 per cent in over 4,000 tests. The mean difference obtained by us in 530 tests was 7.5 per cent. In table 2, the disparity between the pairs of observations on the basal metabolic rate is given. Since this is a measure of the accuracy of clinical calorimetry, it is impossible to obtain a greater degree of accuracy with any formula. For comparison we indicate the agreement between the rate calculated by our formulas and the rate determined in the laboratory. In each column the accuracy of prediction of the formulas is only slightly less than the accuracy of the test of the metabolic rate itself. Consequently we believe that the formulas give results that are almost as good as can be obtained until a more satisfactory method of determining the metabolic rate is available.

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20. Gephart, F. C., and DuBois, E. F.: Clinical Calorimetry: IV. Arch. Int. Med. **15**:835 (June) 1915.

21. Wishart, G. M.: The Variability of Basal Metabolism, Quart. J. Med. **20**:193, 1927.

22. Jenkins, R. L.: The Error of Basal Metabolism Determination and the Normal Range of Basal Metabolism, Arch. Int. Med. **49**:181 (Feb.) 1932.

It should be stated that the larger deviations between the calculated and the measured rate were in the very low and very high ranges, where the actual figure is less important. It makes little difference in an obviously thyrotoxic patient whether the basal metabolic rate is plus 55 or 65 per cent. Determinations of the metabolic rate are most often resorted to in order to ascertain whether the rate is normal or abnormal. For this purpose, prediction formulas are valuable, as they seldom show an abnormal rate in a normal person.

TABLE 2.—*Comparison of Basal Metabolic Rate by Formula and by Indirect Calorimetry*

	No. of Observations	Error Less Than					Error Over
		5%	10%	15%	20%	25%	25%
Comparison of tracings by indirect calorimetry	530	49	77	90	96	97	3
Agreement between B.M.R. by formula and by calorimetry	276	45	73	88	93	98	2

TABLE 3.*—*Standards for Prediction of the Metabolic Rate According to the Authors' Formulas*

Basal Metabolic Rate	Men	Women
From 14 to 16 years	0.012 × P.R. × P.P. —48	0.011 × P.R. × P.P. —46
From 16 to 18 years	0.013 × P.R. × P.P. —44	0.012 × P.R. × P.P. —42
From 18 to 20 years	0.013 × P.R. × P.P. —41	0.012 × P.R. × P.P. —39
From 20 to 30 years	0.014 × P.R. × P.P. —39	0.013 × P.R. × P.P. —38
From 30 to 40 years	0.014 × P.R. × P.P. —39	0.013 × P.R. × P.P. —37
From 40 to 50 years	0.014 × P.R. × P.P. —38	0.013 × P.R. × P.P. —36
From 50 to 60 years	0.015 × P.R. × P.P. —36	0.013 × P.R. × P.P. —34
From 60 to 70 years	0.015 × P.R. × P.P. —34	0.014 × P.R. × P.P. —32
From 70 to 80 years	0.016 × P.R. × P.P. —32	0.014 × P.R. × P.P. —30

* The data for this table are calculated on the Sage normal standards (DuBois, E.: Basal Metabolism in Health and Disease, Philadelphia, 1927, p. 200). The standards differ slightly, but not significantly from those of Boothby and Sandiford (Am. J. Physiol. **90**: 291, 1929).

If it is desired to employ the prediction formulas to calculate the basal metabolic rate directly without reference to the normal standards, table 3 may be used. It is derived from the formulas presented here and takes cognizance both of age and of sex.

SUMMARY

A new method for the derivation of formulas for predicting the basal metabolic rate from pulse rate and pulse pressure is reported.

The accuracy of the new formulas is compared with that of certain former ones.

The inaccuracy of the determination of basal metabolism by indirect calorimetry is pointed out.

The accuracy of the new formulas is shown to compare favorably with the accuracy of clinical calorimetry.

CONCLUSIONS

These formulas are valuable for (1) estimating the basal metabolic rate if the facilities for measuring the consumption of oxygen are not available and (2) checking the reliability of the metabolic rate as determined by indirect calorimetry. If there is a marked disparity between the results obtained by the two methods the test should be repeated. In many cases the metabolic rate predicted by the pulse rate and pulse pressure obtained in the morning before the patient arises may be more accurate than the rate determined by measuring the consumption of oxygen after the patient has arisen, dressed and traveled to a laboratory.

CHANGES IN TEMPERATURE OF THE SKIN FOLLOWING THE INGESTION OF FOOD

GEORGE BOOTH, M.D.
AND
JAMES M. STRANG, M.D.
PITTSBURGH

The weight of a person is dependent on the balance of the intake and the output of energy. There is, however, no information which explains why some persons are contented with an intake equal to their energy output while others choose an excessive or a deficient intake of food. It is possible that the sensation of satiety is the controlling factor in making this choice. The physiologic reactions which are the components of this sensation have not been fully established. The production of heat resulting from the ingestion of food is well known, and it is conceivable that the sudden change in the rate of production of heat by the body during a meal may bear some relation to the sensation of satiety. The disposition of the heat, particularly its dissipation, may be of importance in this relationship. One factor of the dissipation of heat is reflected in the changes in the temperature of the skin. This report describes observations on skin temperature and blood pressure following a meal of meat which was designed to attain satiety.

No previous studies bearing on this point have been noted in the literature. Talbot [1] and McClure and Sauer [2] reported observations on the temperature of the skin of infants which extended over a feeding period. They observed no change in the temperature in response to the food. No descriptions of the meals were given, and it is assumed that they were ordinary feedings not particularly designed to cause satiety. Keller [3] reported a single observation of a rise of 3 C. in the arm following a meal. Here, again, the meal was not described.

METHOD

The meal used was designed to attain satiety as quickly as possible and to yield a maximum production of heat. Ground beefsteak, with sufficient stewed

From the Medical Service of the Western Pennsylvania Hospital.

1. Talbot, F. B.: Skin Temperatures of Children, Am. J. Dis. Child. **42**:965 (Oct.) 1931.

2. McClure, W. B., and Sauer, L. W.: The Influence of Clothing on the Surface Temperature of Infants, Am. J. Dis. Child. **10**:425 (Dec.) 1915.

3. Keller, C., quoted by Cobet, R.: Die Hautemperatur des Menschen, Ergebn. d. Physiol. **25**:439, 1926.

tomatoes to render it palatable, was the meal chosen. The subjects were requested to eat as much as they could possibly consume, using as much time as they desired to do so.

The temperature of the skin was determined with a Tycos dermotherm [4] at the palm of the hand and the ball of the thumb and at the sole of the foot and the ball of the great toe. These points were chosen because in our preliminary observations of fifteen of the points described by Benedict [5] these four points showed the maximum variations in temperature. At the start of a test period, preliminary readings were taken until the temperature became stabilized at each point. This usually required from ten to twenty minutes after the acclimatization of the subject. For each observation readings were then taken at each point until constant within 0.1 C., usually from two to four readings. The average of the readings was taken for each point, and the average of the four points was taken for each time interval. The cycle of observations was repeated at two minute intervals for approximately one hour. It was impossible to continue the observations for a longer period because of the appearance of restlessness on the part of the subjects as well as fatigue on the part of the observers.

The readings for blood pressure were taken with a mercury manometer by the auscultatory method. Readings were taken at two minute intervals throughout the period of observation.

Environmental conditions were kept constant within prescribed limits. With few exceptions the room temperature throughout each experiment was kept constant within 1 C., the average variation being 0.7 C., at a level which was comfortable for the individual subject. The room temperatures selected ranged from 20 to 25 C. Wet and dry bulb thermometer readings were recorded in most instances, and, as has been observed by others,[2] the humidity, within normal limits, exerted no detectable influence on the temperature of the skin. An electric fan running at a constant speed was placed in a distant part of the room in order to insure a uniform circulation of air. The subject was protected from currents of wind by a series of screens. He was seated in a comfortable chair with the legs resting on a stool, so that the feet were on a level with the seat of the chair. Both arms and both legs were exposed equally throughout the preliminary period and the test period. All tests were done at 4 o'clock in the afternoon, and the subject had fasted since breakfast on the day of the test.

The subjective and objective symptoms experienced by the subjects were recorded at the time of their appearance. Those encountered were a feeling of warmth, the appearance of gross perspiration, a feeling of drowsiness, sleep and finally restlessness.

Twenty-one observations were made on persons of normal weight. The subjects were all within a range of from 90 to 110 per cent of their theoretically ideal weight and were free from any detectable disease.

Seventeen observations were made on persons who weighed more than 110 per cent of their theoretically ideal weight, the minimum being 111 per cent, the maximum 194 and the average 149.

Two types of control observations were carried out. Five of the persons of normal weight and three of the obese subjects were observed under the standard conditions of the test except that the meal was omitted. The effects of

4. The observations were made with a Tycos dermotherm, which was supplied by the Taylor Instrument Company, Rochester, N. Y.

5. Benedict, F. G.: Measurement of the Skin Temperature of Humans, Leopoldina, no. 4, 1929, p. 129.

variation in room temperature, insufficient acclimatization of the subjects and fatigue were observed in two of the subjects. The base line curve was obtained from the other six.

Three of the subjects of normal weight were observed while eating a meal of meat which did not attain the level of satiety.

With these standards established, certain of the experimental and control observations were discarded. Two of the experimental and one of the control observations were discarded because of sudden variations in room temperature which seemed to have a direct effect on the temperature of the skin. One control observation was discarded because the acclimatization of the subject was not complete. A single point, the great toe, was unusually cold at the onset, and suddenly warmed, some time after the temperature had apparently reached a stable level, causing a rise of 2.5 C. in the average curve. Another control observation was discarded because of subjective cooling during the period of observation, accompanied by a sharp fall in the temperature of the skin. One subject of the experimental series was found to have a blood pressure of 190 systolic and 110 diastolic. This record was omitted in order to avoid the possibility of a complicating factor in the vascular disease. Another subject in the experimental series experienced a violent emotional storm in her endeavor to outstrip one of her fellow patients in eating ability. The systolic blood pressure rose 50 mm., and the temperature of the skin rose 1.6 C. in two minutes. This record was omitted. There was one "sport" in the entire group. The deviation of the temperature of the skin from the mean was greater than four times the average deviation from the mean. This record was omitted.[6]

For purposes of analysis the data obtained were charted in graphs, with the numbers of grams of meat eaten, the systolic and diastolic blood pressure in millimeters of mercury and the temperature of the skin to 0.1 C. as ordinates, and the time intervals, two minutes, as abscissas. Such graphs were constructed for each individual experiment. Composite graphs were then made of the reactions of the normal, the obese and the control groups. On the graphs certain particular time intervals were marked off, namely, the start of the meal, the completion of the meal and the point of maximum variation of the temperature of the skin. The appearance of subjective or objective symptoms was also noted.

OBSERVATIONS

Subjects of Normal Weight.—Nineteen acceptable observations were made on seventeen persons of normal weight. The average amount of meat eaten was 505 Gm., the maximum was 900 Gm. and the minimum was 150 Gm. Only five of the nineteen subjects ate less than 400 Gm. The average time of eating was twenty-two minutes, the maximum was thirty-six minutes and the minimum was twelve minutes.

A composite curve of the temperature reactions of the skin of the group showed a rise shortly after the start of the meal and a steady rapid increase for forty minutes. This was followed by a further slight increase to the maximum elevation in sixty minutes (chart 1). The earliest onset of the reaction was four minutes, the latest thirty-six minutes and the average ten minutes. The minimum elevation was +0.9 C., the maximum +4.7 C. and the average 2 C. Sixteen of the nineteen exhibited reactions which corresponded to the average pattern of the curve.

6. Goodwin, H. M.: Precision of Measurements and Graphical Methods, New York, McGraw-Hill Book Company, 1913, p. 21.

The composite curve of the blood pressure showed a rise of 10 mm. of mercury, both systolic and diastolic, at the start of the meal and a return to normal at its completion. This reaction was uniform throughout the series.

In three subjects in the series the experiment was repeated after an interval of two years, and the results in two instances were remarkably similar. The meat eaten by one subject (table 1, case 1) amounted to 500 Gm. and 650 Gm., respectively, the initial rise in temperature of the skin occurred in ten minutes

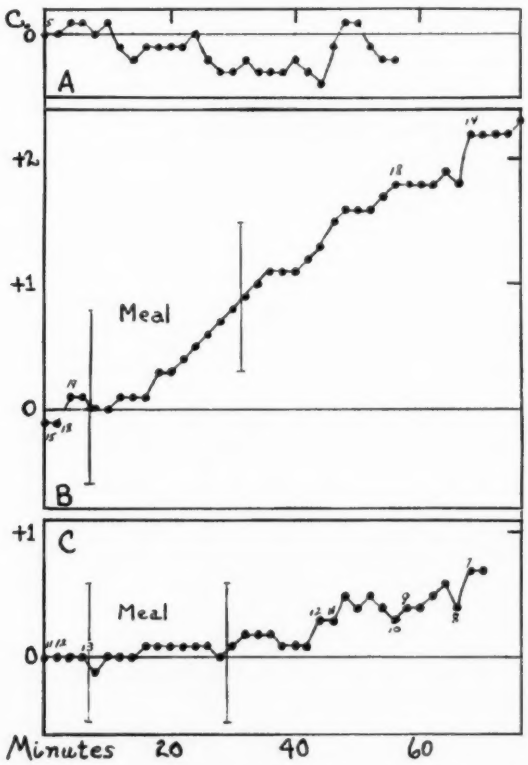

Chart 1.—Composite curves of the temperature reactions of the skin during the control period with the meal omitted (*A*) and of persons of normal weight (*B*) and obese persons (*C*) before, during and after a meal of meat to the level of satiety.

and twelve minutes, and in each experiment the maximum elevation was +2.6 C. The meat eaten by another (table 1, case 2) amounted to 600 Gm. in each experiment, the initial reaction occurred in eighteen and twelve minutes, respectively, and the maximum elevations were +4.1 C. and +4.6 C. The reaction of the third subject differed only in intensity (table 1, case 3). The meal eaten amounted

to 700 Gm. in both tests, the initial rise in the temperature of the skin occurred in thirty-four and six minutes, respectively, and the maximum elevations of temperature were +0.7 C. and +1.9 C.

Obese Subjects.—Fourteen acceptable observations were made on eleven obese persons. The average amount of meat eaten was 490 Gm., the maximum was 1,050 Gm. and the minimum was 150 Gm. Four of the thirteen subjects ate less than 400 Gm. The average time of eating was twenty minutes, the maximum thirty-six minutes and the minimum fourteen minutes.

A composite curve of the temperature reactions of the skin showed a rise beginning a considerable time after the start of the meal and a relatively small maximum elevation (chart 1). The most rapid onset of the reaction was after four minutes, and the most delayed onset was after forty-six minutes. The average was twenty-four minutes. The maximum elevation was +3.7 C.; the maximum drop in temperature was —2.1 C., and the average change was only +0.6 C.,

TABLE 1.—*Original Observations and Those Made Several Years Later*

Case	Date	Percentage of Ideal Weight	Surface Area, Sq. M.	Meat Meal, Gm.	Time of Initial Change in Skin Temperature, Minutes	Maximum Change in Skin Temperature, C.	Time of Maximum Change in Skin Temperature, Minutes
1	11/13/31	102.6	1.85	500	10	+2.6	44
	11/19/33	100.0	1.84	650	12	+2.6	38
2	11/18/31	96.6	1.75	600	18	+4.1	64
	11/19/33	98.0	1.76	600	12	+4.6	82
3	11/17/31	94.0	1.82	700	34	+0.7	54
	11/20/33	94.0	1.82	700	6	+1.9	38
4	11/24/31	171.7	2.04	400	2	—0.5	30
	11/27/33	178.6	2.09	550	28	—1.0	44
5	12/ 1/33	150.5	1.95	750	4	+3.6	46
	1/16/34	131.4	1.85	600	8	+1.1	72
6	12/ 1/31	110.7	1.72	750	46	—1.0	64
	12/13/33	104.9	1.67	900	4	+4.2	64
7	11/11/31	116.8	2.11	500	8	+0.5	22
	12/ 3/33	108.8	2.05	900	14	+1.3	50

in contrast with 2 C. in the group of normal weight. Six of the fourteen failed to show the characteristic pattern of curve.

A composite curve of the blood pressure in this group showed a prompt rise of 10 mm. of mercury, both systolic and diastolic, and a return to the previous level at the completion of the meal. There was no difference in the response of the blood pressure in the two groups.

The experiment was repeated with four subjects in this series, and in three instances the resulting curves were similar in contour to the first one (table 1). The meat eaten by one subject (case 4, table 1) amounted to 400 Gm. and, two years later, 550 Gm. The initial rise occurred in two and twenty-eight minutes, respectively, and the maximum variation in temperature was —0.5 C. and —1 C. The meat eaten by the second subject (table 1, case 5) amounted to 750 Gm. and, one month later, 600 Gm. The initial reaction occurred in four and eight minutes, respectively, and the maximum change was +3.6 C. and +1.1 C. The third subject (table 1, case 7) ate 500 Gm. of meat at the first test and 900 Gm. two years later at the second test. The initial changes in the temperature of the skin occurred in eight and fourteen minutes, respectively, and the maximum changes

were +0.5 C. and +1.3 C. There was a change in the reaction on the second test of the fourth subject (table 1, case 6). The subject first ate 750 Gm. of meat and two years later 900 Gm. The initial changes in the temperature of the skin occurred in forty-six and four minutes, respectively, and the maximum changes were —1 C. and +4.2 C.

Control Group.—Acceptable observations were made on two persons of normal weight and three obese persons with the meal omitted (chart 1). A composite curve of the temperature reactions of the skin of the control group showed a fall of 0.2 C. in fifty-six minutes. The maximum elevation was +0.9 C., and the maximum drop was —1.2 C. The reaction followed the same pattern in both the persons of normal weight and the obese subjects.

The blood pressure showed no variation throughout the observation period.

Three persons of normal weight, who had previously served as subjects for the experiments on satiety and had exhibited reactions which followed the normal pattern of the curve, were observed during a meal of meat which did not attain the level of satiety. In each instance the temperature reaction of the skin was decidedly less intense than the reaction to the satiety meal. The data obtained are included in table 2.

TABLE 2.—*Observations on Three Persons While Eating a Meal of Meat Below the Level of Satiety*

Meat, Gm.	Time of Initial Change in Skin Temperature, Minutes	Maximum Change in Skin Temperature, C.	Time of Maximum Change in Skin Temperature, Minutes
200	10	—1.8	44
400	16	+0.5	26
450	16	+0.8	30

In the control experiments the blood pressure showed a prompt rise of 10 mm. of mercury, systolic and diastolic, and a return to the previous level at the completion of the meal.

COMMENT

Blood Pressure.—In all experiments, in the persons of normal weight as well as in the obese subjects, the blood pressure reaction was uniform. There was a rise in blood pressure immediately following the start of the meal and a return to the previous level immediately following the completion of the meal. The reaction seemed to be related to the exertion of eating rather than to the characteristics of the subjects or of the meals.

Meal.—It may be noted that the average meal eaten by the group of normal weight appears to have been slightly larger than that of the obese group. This difference is due to the uneven distribution of the sexes in the two groups. The men in both groups consumed an average of 619 Gm. of meat, whereas the women averaged only 420 Gm. This sex difference was characteristic of both the obese group and the group of normal weight, as will be described later. The obese group was

composed of four men and ten women, whereas there were nine men and ten women in the group of normal weight, which precludes a direct comparison of the unweighted average figures for intake of food of the two groups.

Skin Temperature.—It should be emphasized that our interest was in the variation in the temperature of the skin over a short period rather than in the actual level of the temperature. With the precautions observed, we think that the reactions are sufficiently uniform to justify consideration. Additional evidence of the uniformity of the reaction is offered by the repetition of the observations on seven of the subjects (table 1). For four of the seven the contour of the curves corresponded closely. At the time of the original observations on two of the remaining subjects they were classified as mildly obese, and the temperature reactions of the skin corresponded to those exhibited by the obese group. Before the second observations were made they had reduced to 105 and 109 per cent of their theoretical ideal weight. At this time both reactions corresponded to the normal. In one instance there was a change in the character of the reaction without any change in weight (table 1, case 3). No explanation of this reaction is offered.

The two points of particular interest in a comparison of the reactions of the persons of normal weight and those of the obese group are the difference in the magnitude of the elevation of skin temperature and the difference in the time of its occurrence. In regard to magnitude, an isolated observation of a difference of 1.4 C. might not be remarkable. However, a difference of 1.4 C. between the average figures of eighty readings for each time interval for the group of normal weight and those of fifty-two readings for each time interval for the obese group is significant. The time of the reaction in relation to the meal is perhaps of more significance. The initial reaction was observed in ten minutes in the group of normal weight, in contrast to twenty-four minutes in the obese group. The time relationship is illustrated in chart 2, which shows composite curves of the observations during the control period, during the meal and after the completion of the meal, in separate phases.

In the group of normal weight, ten minutes after the beginning of the meal there was a rise in the temperature of the skin which continued and amounted to 0.9 C. in twenty-two minutes when eating stopped. There was a further steady increase to 1.8 C. in forty minutes. The maximum elevation of 2 C. was attained in the third twenty minute period.

In the obese group the elevation of the temperature of the skin at the time of cessation of eating, twenty minutes after the meal was begun, was only 0.1 C. After the period of eating there was a further rise to the maximum of 0.5 C. in forty minutes. This level was main-

tained without essential change during the next twenty minutes of observation. The elevation of only 0.1 C. during the period of eating in this group is in marked contrast to the elevation of 0.9 C. in the group of normal weight.

Surface Area.—In view of the relationship between the surface area and the metabolism of a subject, that property might be expected to be a factor of influence in the phenomenon reported here. The average surface area of the group of normal weight was 1.67 square meters ± 0.15 (table 3). In the obese group the average area was 2.01 square meters ± 0.11. If the two groups are each subdivided into one group with reactions which followed the average pattern and another group

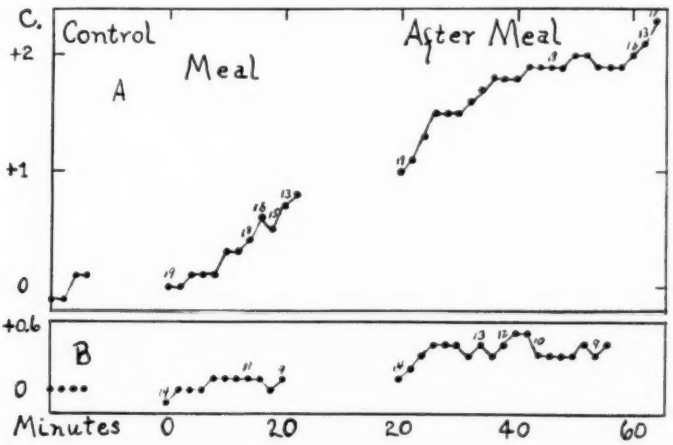

Chart 2.—Composite curves showing the relation of the magnitude of the elevation of the temperature of the skin and the time of its occurrence in persons of normal weight (*A*) and obese persons (*B*) during the control period and during and after the meal.

with reactions which failed to follow the average pattern, the exact importance of the factor of surface area may be more clearly defined. In the group of normal weight the reactions of sixteen subjects followed the average pattern, and the average surface area was 1.69 square meters ± 0.15. The average area of the four whose reactions failed to follow the average pattern was 1.58 square meters ± 0.16 (table 3).

In the obese group the average surface area of the seven subjects whose reactions followed the average pattern was 2.08 square meters ± 0.10. The average area of the remainder of the group was 1.94 square meters ± 0.13.

The individual curves did not bear any relationship to the corresponding individual surface areas. Some of the higher elevations of skin temperature occurred in subjects with large surface area, and some of the more pronounced instances of lowering of the temperature occurred in persons with a small surface area in both the subjects of normal weight and the obese group. For example, in the group of normal weight the two subjects with the largest surface area, 1.9 and 1.85 square meters, each had an elevation of temperature of + 2.6 C., whereas the two subjects with the smallest surface area, 1.36 and 1.39 square meters, had elevations of + 1.8 C. and + 1.4 C. In the obese group the two subjects with the largest surface area, 2.4 and 2.14 square meters, had elevations of temperature of + 0.7 C. and + 3.6 C., whereas the two subjects with the smallest surface area, 1.7 and 1.81 square meters, had elevations of temperature of + 1.8 C and — 1.2 C. It

TABLE 3.—*The Surface Area in Relation to Changes of Temperature of the Skin*

	Subjects	Surface Area, Sq. M.	Average Deviation from Mean
Normal group	19	1.67	±0.15
Obese group	14	2.01	±0.11
Normal group with normal reaction	15	1.69	±0.15
Normal group with no elevation of skin temperature	4	1.58	±0.16
Obese group with obese reaction	8	2.08	±0.10
Obese group with elevation of skin temperature	6	1.94	±0.13

appears, therefore, that the surface area is not the controlling factor in the reaction.

Sex Difference.—On analysis for other possible factors of influence, it was observed that there was a slight but consistent difference in the magnitude of the reaction in the two sexes (chart 3). In the group of normal weight the meals taken by the ten women averaged 365 Gm. of meat, with a minimum intake of 150 Gm. and a maximum of 900 Gm. The nine men in the group of normal weight took an average of 633 Gm. of meat, with a minimum of 500 Gm. and a maximum of 900 Gm. The average elevation of the temperature of the skin of the women was + 1.6 C., the minimum + 1.1 C. and the maximum + 4.6 C. The average elevation of the temperature of the skin of the men was + 2.1 C., the minimum + 0.9 C and the maximum + 4.7 C.

In the obese group, ten women ate an average of 475 Gm. of meat. The minimum was 150 Gm., and the maximum was 750 Gm. In the same group, the four men ate an average of 588 Gm. of meat. The minimum was 300 Gm., and the maximum was 1,050 Gm. The elevation

of temperature among the women was: average + 0.4 C., minimum — 2.1 C. and maximum +3.7 C. In the group of obese men the average elevation of temperature was + 1.2 C., the minimum + 0.3 C. and the maximum + 2.4 C.

A comparison of the meals eaten by the two groups brings out the fact that the ten obese women ate a considerably larger meal than the ten women of normal weight. In the case of the men the average of nine persons of normal weight was slightly higher than that of the

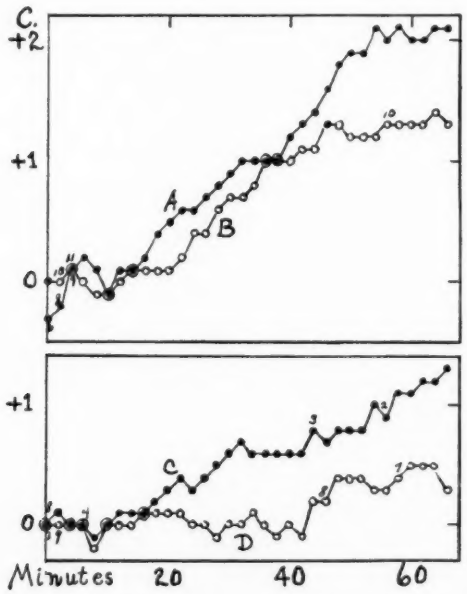

Chart 3.—Composite curves showing the difference in the magnitude of the temperature reaction of the skin between the sexes. *A* is the curve for men of normal weight; *B*, for women of normal weight; *C*, for obese men, and *D*, for obese women.

obese men, but there were only four of the latter, not a large enough group to offer comparable figures.

Relation of Changes in Temperature of the Skin to Satiety.—In these experiments the attainment of satiety, as evidenced by the cessation of eating, was also marked by a sensation of warmth in most cases and by the appearance of gross perspiration in some. These phenomena emphasize the importance of the production and dissipation of heat in the response of the body to the ingestion of food. In studies of the

specific dynamic action of food, Strang and McClugage [7] emphasized the physiologic load thrown on the body in normal persons by the rapid change in the production of heat resulting from the ingestion of food. One aspect of the physiologic dissipation of the extra heat is described by the observations on the temperature of the skin. The rapid change in temperature is probably responsible for the sensation of warmth usually experienced, as it has been demonstrated by Bazett [8] that this sensation is the result of the rate of change of the temperature of the tissues surrounding the nerve end-organs in the skin rather than the result of changes in the actual temperature of the tissues. Accordingly, it is conceivable that the intensity of the sensation of warmth may be one important component of the sensation of satiety. Certainly in persons of normal weight the inability to continue eating coincided with a rise of 0.9 C. in only twenty-two minutes.

In obese subjects the total production of heat in response to food is probably the same as in persons of normal weight. Although the total production of heat is the same, studies of the specific dynamic action [7] showed a slower rate of change of the rate of production of heat and, furthermore, the maximum point of the rate of change was definitely delayed. This phenomenon is conceivably reflected in the diminished and delayed elevation of the temperature of the skin in the obese subjects reported on here. The resulting decrease in the intensity of the sensation of warmth may be one factor in the delay of the sensation of satiety, permitting the consumption of food in excess of the actual physiologic requirement.

CONCLUSIONS

Observations on the blood pressure and the temperature of the skin after a meal of meat designed to attain satiety were made on nineteen persons of normal weight and fourteen obese subjects.

The response of the blood pressure was identical in the two groups and probably due solely to the work of eating.

In the group of normal weight there was an elevation of the temperature of the skin, which began shortly after the start of the meal and reached a maximum of 2 C. in sixty minutes.

The elevation of the skin temperature in the obese group was definitely diminished and delayed as compared with that of the group of normal weight.

It is suggested that the difference in reaction may be one factor in the delayed sensation of satiety in obese persons and therefore a controlling factor in the determination of the large intake of obese persons.

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7. Strang, J. M., and McClugage, H. B.: The Specific Dynamic Action of Food in Abnormal States of Nutrition, Am. J. M. Sc. **182**:49, 1931.

8. Bazett, H. C.: Physiological Responses to Heat, Physiol. Rev. **7**:531, 1927.

CLINICAL VALUE OF THE TEST FOR HIPPURIC ACID IN CASES OF DISEASE OF THE LIVER

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A satisfactory test of the function of the liver should (1) detect and estimate hepatic insufficiency, (2) aid in a differential diagnosis, (3) have prognostic usefulness and (4) contribute toward a better understanding of the physiology of the liver. With these objectives, the synthesis of hippuric acid: (benzoic acid + amino-acetic acid = hippuric acid) was studied both experimentally and clinically.[1] It was observed that the hourly rate of excretion of hippuric acid in normal persons following the ingestion of sodium benzoate is remarkably constant, being influenced only somewhat by the size of the subject or, more exactly, by the surface area. In certain types of disease of the liver, however, the output of hippuric acid is markedly reduced. This reduction is due primarily to the diminished capacity of the liver to synthesize amino-acetic acid and in part to damage of the enzymatic mechanism which unites benzoic acid with amino-acetic acid. In man, as in the rabbit, this conjugating enzyme is present mainly in the liver, and the small amount which occurs in the kidneys is insufficient to compensate when injury to the liver occurs. The output of hippuric acid after the ingestion of benzoic acid can therefore be considered a measure of the liver's capacity to furnish amino-acetic acid and also an index of its detoxifying power. Fortunately, the adaptation of this test for clinical use presents no difficulties, since both the procedure for carrying out the test on the patient and that for determining the amount of hippuric acid in the urine are simple and require no elaborate equipment. Since the first report the test has been applied in a larger

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1. Quick, A. J.: The Study of Benzoic Acid Conjugation in the Dog with a Direct Quantitative Method for Hippuric Acid, J. Biol. Chem. **67**:477 (Feb.) 1926; The Conjugation of Benzoic Acid in Man, ibid. **92**:65 (June) 1931; On the Chemistry of the Conjugation of Benzoic Acid, ibid. **95**:189 (Feb.) 1932; The Site of the Synthesis of Hippuric Acid and Phenylacetic Acid in the Dog, ibid. **96**:73 (April) 1932. Quick, A. J., and Cooper, M. A.: The Effect of Liver Injury on the Conjugation of Benzoic Acid in the Dog, ibid. **99**:119 (Dec.) 1932; The Synthesis of Hippuric Acid: A New Test of Liver Function, Am. J. M. Sc. **185**:630 (May) 1933.

number of cases, comprising a sufficient variety of pathologic changes in the liver to enable one to make a more accurate evaluation of its clinical usefulness.

PROCEDURE

One hour after a light breakfast of coffee and toast the patient is given 6 Gm. of sodium benzoate dissolved in 30 cc. of water, preferably flavored with oil of peppermint. This is followed by one-half glass of water. Immediately after taking the drug the patient voids, and he then collects complete specimens of urine hourly for four hours. Should the analysis be delayed more than ten hours, the samples are preserved with toluene. The specimen for each hour is measured and transferred to a beaker. If the volume of any specimen exceeds 100 cc., it is acidified with a few drops of acetic acid and concentrated in a water bath to about 50 cc. Each of the four specimens is acidified with 1 cc. of concentrated hydrochloric acid and then tested with congo red paper. If the paper does not turn blue more acid must be added. Each specimen is vigorously stirred until the precipitation of hippuric acid is complete and then is allowed to stand for one hour at room temperature. The crystalline hippuric acid is filtered off on a small filter plate or Buchner funnel, washed with a small quantity of cold water and allowed to dry in the air. The dry samples of hippuric acid are weighed (to the second decimal place is sufficiently accurate). If a balance is not available, the precipitate may be dissolved in hot water and titrated with two-tenths normal sodium hydroxide, phenolphthalein being used as an indicator (1 cc. = 0.0358 Gm. of hippuric acid). To the amount of hippuric acid determined by weight or titration one adds the amount remaining dissolved in the urine. This can readily be calculated, since 100 cc. of urine at room temperature will dissolve 0.33 Gm. of hippuric acid. Thus, for example, if the hourly specimen amounts to 70 cc. and the amount of hippuric acid obtained by weight is 1.1 Gm., the total will be 1.1 plus (0.33 Gm. $\times$ $\frac{70}{100}$) or 1.33 Gm. of hippuric acid. To express this result in terms of benzoic acid, one multiplies by the factor 0.68. Therefore, 1.33 Gm. $\times$ 0.68 equals 0.91 Gm. of benzoic acid.

The normal adult will excrete about 3 Gm. of benzoic acid in the form of hippuric acid in four hours. Therefore, 3 Gm. has been taken as the normal value for calculating the efficiency of the liver. On this basis the normal range is from 85 to 110 per cent. This provides for the variation due to the size of the individual patient.

OBSERVATIONS ON PATIENTS WITH VARIOUS CONDITIONS

Catarrhal Jaundice.—This common but ill defined clinical condition invariably causes a marked impairment of liver function, as shown in table 1. The observations are in accord with the modern view that the condition is a type of intrahepatic jaundice in which the primary dysfunction is in the parenchymal cell. The results of the test for hippuric acid run roughly parallel with the clinical course. Without special treatment, recovery occurs in from four to six weeks, and at this time the synthesis of hippuric acid is normal. The patient in case 6, who was intensively treated according to the routine, which will be discussed later, recovered promptly, and the reaction became normal in less than two weeks after the onset of the jaundice.

Toxic Hepatitis of Known Origin.—With the advent of synthetic coal tar compounds as therapeutic agents, the incidence of hepatitis has greatly increased. Clinically I have found it convenient to divide the acute hepatitis into three types, or, perhaps more correctly, stages. The first is enlargement of the liver, sometimes attended by tenderness but without evidence of jaundice. One can look on it as edema of the liver, probably related to angioneurotic edema. Function may not be appreciably disturbed. In fact, a patient from my previous series who had mild hepatitis without jaundice following treatment with arsphenamine had an increased output of hippuric acid, which suggested abnormal stimulation rather than a depression of function. The second type, which is the most common, shows jaundice and usually enlargement of the liver. Hepatic function is definitely diminished, as illustrated by

TABLE 1.—*Observations on Patients with Catarrhal Jaundice*

Case	Sex and Age, Years	Enlargement of Liver	Jaundice*	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm. 1 Hr.	2 Hr.	3 Hr.	4 Hr.	Total	Percentage of Normal	Comment
1	F. 21	+	83	0.24	0.38	0.37	0.86	1.85	62	
				0.43	0.41	0.87	0.71	2.42	81	2 months later
				0.90	0.91	1.00	0.34	3.15	105	1 month later
2	F. 60	+	70	0.10	0.17	0.41	0.57	1.25	42	
3	F. 21	+	85	0.15	0.21	0.23	0.28	0.87	29	History of an induced abortion 2 months previously
				0.55	0.77	0.63	0.60	2.55	85	1 month later
4	F. 34	+	75	0.17	0.32	0.44	0.68	1.61	54	
5	M. 29	0	++	0.37	0.59	0.63	0.60	2.19	73	
6	M. 60	0	48	0.14	0.46	0.64	0.56	1.80	60	
				0.60	0.78	1.02	0.83	3.23	107	2 weeks later
7	M. 21	0	88	0.21	0.63	0.61	0.43	1.88	63	

* In this and the following tables the figures indicate the icteric index.

the cases in table 2, and in the severe type the function may become very low. The third class is frank yellow atrophy or, perhaps more correctly, massive necrosis of the liver. The condition in case 11 can be considered as bordering on the third stage. Severe hepatitis developed from a single 2 cc. dose of carbon tetrachloride given as an anthelmintic. The patient had disregarded her physician's instructions not to eat after taking the drug, and she had neglected to take a saline cathartic. She was extremely toxic and remained delirious for four days, and deep jaundice developed. The clinical indications of severe hepatitis were corroborated by the exceedingly low output of hippuric acid, which was only 17 per cent of normal. The great reparative power of the liver in youth was well illustrated by the rapid clinical recovery and the relatively speedy return to normal of the function of the liver. The patient was, however, treated intensively. Hepatitis with jaundice developed in case 9 following the administration of eight

TABLE 2.—*Observations on Patients with Hepatitis of Known Origin*

Case	Sex and Age, Years	Enlargement of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm. 1 Hr.	2 Hr.	3 Hr.	4 Hr.	Total	Percentage of Normal	Comment
8	F. 60	++	0	0.12	0.34	0.52	0.39	1.37	46	Neocinchophen, complicated by cardiac condition
				0.35	0.46	0.63	0.67	2.11	70	1 month later, after treatment
				0.24	0.47	0.53	0.48	1.72	57	6 months later
9	F. 35	++	+	0.31	0.54	0.43	0.44	1.72	57	After 8 doses of neoarsphenamine
10	F. 52	0	0	0.52	0.72	0.65	0.75	2.64	88	6 months after recovery from cinchophen hepatitis
11	F. 21	+	++	0.07	0.14	0.21	0.10	0.52	17	After 2 cc. of carbon tetrachloride
				0.33	0.49	0.90	0.89	2.61	87	7 weeks later; clinically well
12	M. 41	+	70*	0.30	0.58	0.61	0.71	2.20	73	After neoarsphenamine
13	M. 26	+	++	0.50	0.86	1.35	0.35	3.06	102	Jaundice persisting 2 months after 2 injections of arsphenamine

TABLE 3.—*Observations on Patients with a Malignant Process with Metastasis to the Liver*

Case	Sex and Age, Years	Enlargement of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm. 1 Hr.	2 Hr.	3 Hr.	4 Hr.	Total	Percentage of Normal	Comment*
14	F. 53	+	0	0.17	0.50	0.61	0.62	1.90	63	Empyema of gallbladder with beginning malignant process (S)
15	F. 65	++	10	0.24	0.45	0.50	0.47	1.66	55	Malignant process with metastases to liver (C)
16	M. 70	++	0	0.26	0.57	0.71	0.74	2.28	76	Carcinoma of gallbladder and liver (S)
				0.15	0.25	0.41	0.29	1.10	37	1 month later
17	F. 67	++	0	0.26	0.46	0.57	0.61	1.90	63	Adenocarcinoma of ovary with metastasis to liver (S)
18	M. 62	++	15	0.22	0.66	0.65	0.77	2.30	77	Carcinoma of pancreas with metastasis to liver (S)
19	M. 53	++	++	0.19	0.42	0.55	0.58	1.74	58	Carcinoma of stomach with metastasis to liver (A)
20	M. 50	++	120	0.16	0.30	0.39	0.39	1.24	41	Carcinoma of the head of pancreas (S)
21	M. 59	++	75	0.11	0.13	0.27	0.12	0.63	21	Generalized carcinomatosis involving liver (A)
22	F. 50	+	0	0.14	0.34	0.61	0.45	1.54	51	Abdominal neoplasm with metastasis to liver (C)
23	F. 49	0	0	0.51	0.58	0.48	0.54	2.11	70	Carcinoma of ascending colon with adhesion to liver (S)
24	M. 48	++	0	....	1.02	1.63	0.65	3.30	110	Carcinoma of transverse colon with metastasis to liver (S)
25	F. 65	++	0	0.24	0.62	0.30	0.40	1.56	52	Carcinoma of colon with metastasis to liver (S)
26	M. 61	++	60	0.15	0.46	0.57	0.46	1.64	55	Carcinoma of stomach with metastasis to liver (S)

* In this and the following table the letters in parentheses indicate the method of making the diagnosis: clinically (C), surgically (S) or at autopsy (A).

0.3 Gm. doses of neoarsphenamine. On investigation of the patient's previous record, it was found that a Wassermann reaction which was anticomplementary had been erroneously interpreted as positive. There was no evidence either clinically or serologically that the patient ever had syphilis. One can therefore look on this case as further evidence for the view that the arsphenamine group of compounds can cause damage to the liver in the absence of the predisposing influence of syphilis.

Malignant Processes; Metastasis to the Liver.—In all but one of the twelve cases of a malignant process, given in table 3, there was a definite diminution of function according to the test for hippuric acid. The one exception is hard to explain. It seems probable that the disturbance of function is due primarily not to a destruction of parenchymal tissue but rather to the toxins arising from the malignant process. The results of the test appear to run fairly parallel with the clinical condition of the patient. This was illustrated by the patient in case 16, who at the time of his admission to the hospital showed few signs of cachexia and a function 76 per cent of normal. In the course of one month his condition declined rapidly from a clinical point of view, and the hepatic function dropped to 36 per cent.

Cholecystitis and Cholelithiasis.—Since cholecystitis is essentially an extrahepatic condition, it is to be expected that liver function will not be greatly disturbed. Both in the present series (table 4) and in an earlier group it was noted that the production of hippuric acid was not impaired in cases of cholecystitis; in fact, a number of patients actually showed an abnormally large output. Likewise, obstruction of the common duct by stones, even with a long history of intermittent jaundice, caused no definite impairment of liver function. Vaccaro [2] recently made an interesting study of cholecystitis, correlating the output of hippuric acid with the gross appearance of the liver noted at operation. He observed a fairly close relationship between the results of the test for function and the degree of cirrhosis grossly discernible. From the results obtained by the test for hippuric acid, one can conclude that cholecystitis usually causes little or no diminution of hepatic efficiency and that even obstruction due to a stone in the common duct will have little effect on the liver unless the blockage is complete and unduly prolonged.

Miscellaneous Hepatic Diseases.—Three patients with atrophic cirrhosis had a marked diminution of function as measured by the synthesis of hippuric acid. The patient in case 47 had also thrombocytopenic

2. Vaccaro, P.: The Synthesis of Hippuric Acid: Its Value in Detecting Hepatic Damage Secondary to Diseases of the Extrahepatic Biliary System, Surg., Gynec. & Obst. **61**:36 (July) 1935.

purpura, which responded to splenectomy, but the patients in cases 48 and 49 had typical advanced Laënnec cirrhosis with ascites. Cases 50, 51 and 52 were classified as hypertrophic cirrhosis of unknown origin. The difficulty of arriving at a satisfactory diagnosis is illustrated by the remaining cases in table 5. In case 53 there was a history of recurring attacks of jaundice, with nausea and vomiting, and a marked loss of weight. The patient presented the picture of a toxic rather than an obstructive type of jaundice. It is difficult to decide whether case 54 represents syphilitic cirrhosis or arsphenamine hepatitis. The patient

TABLE 4.—*Observations on Patients with Cholecystitis and Cholelithiasis*

Case	Sex and Age, Years	Enlargement of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm. 1 Hr.	2 Hr.	3 Hr.	4 Hr.	Total	Percentage of Normal	Comment
27	F. 39	0	0	0.73	0.99	1.12	0.75	3.59	120	Cholecystitis (S)
28	F. 41	0	0	0.31	0.81	0.99	0.69	2.80	93	Cholecystitis (S)
29	F. 65	0	0	0.52	1.14	1.38	0.37	3.41	114	Cholecystitis (S)
30	F. 50	0	0	0.46	0.71	0.67	0.82	2.66	89	Cholelithiasis (x-ray); nephrectomy 14 years previously
31	M. 56	0	0	0.22	0.40	0.90	0.83	2.35	78	Cholelithiasis (x-ray)
32	M. 65	0	0	0.60	0.88	0.99	0.91	3.38	113	Cholecystitis (C)
33	M. 54	+	0	0.43	0.75	0.90	0.66	2.74	91	Cholelithiasis and abscess of liver (S)
34	M. 31	0	0	0.53	0.64	0.94	0.78	2.89	96	Cholecystitis (S)
35	F. 52	0	0	0.34	0.60	0.78	0.73	2.45	82	Pain in upper quadrant on right; cholecystectomy 5 years before
36	M. 36	0	0	0.69	0.77	0.53	0.71	2.70	90	Cholecystitis (C)
37	F. 53	0	0	0.23	1.17	1.38	0.17	2.95	98	Cholecystitis (C) and asthma
38	F. 54	0	30	0.33	0.76	1.15	0.92	3.16	105	Large stone of common duct; liver appeared normal (S)
39	M. 49	0	19	0.59	0.75	0.88	0.91	3.13	104	Stone of common duct (S)
40	F. 50	0	9	0.28	1.08	0.67	0.63	2.66	89	Cholecystitis (C)
41	M. 53	0	0	0.50	0.93	0.86	1.07	3.76	125	Cholecystitis (C)
42	F. 37	0	0	0.24	0.84	0.83	0.79	2.70	90	Cholecystitis (C)
43	F. 26	+	0	0.75	0.74	0.71	0.92	3.10	103	Cholecystitis (C)
44	F. 37	+	15	0.10	1.03	1.23	1.04	3.40	113	Cholecystitis (C) and cholelithiasis; slight obstruction of common duct (S)
45	M. 57	0	0	0.27	0.65	0.93	0.93	2.78	93	Cholecystitis (S)
46	F. 25	0	0	0.55	0.81	0.80	0.41	2.57	86	Cholecystitis and cholelithiasis; liver appeared normal (S)

in case 55 had toxemia of pregnancy and showed a moderate impairment of liver function. The patient in case 56 had primarily a cardiac disturbance, but it is probable that she had a septic process, as indicated by the chart for the temperature, and that sepsis was responsible for the mild jaundice and the decrease in liver function. Transient jaundice, such as was observed in case 57 following an appendectomy, was not accompanied by demonstrable impairment of liver function. The patient in case 58 presented a very puzzling condition. She had severe diarrhea, a slightly enlarged liver, brown pigmentation, especially on her legs, an icteric index of 60 and no free hydrochloric acid in her stomach. Inter-

estingly, the plasma was markedly anticomplementary.[3] This observation, together with the jaundice, pigmentation and enlargement of the liver indicated a hepatic pathologic process, but a definite diagnosis could not be made. The output of hippuric acid was very low.

The cases listed in table 5 illustrate that hepatic insufficiency, as measured by the test for hippuric acid, is present in a variety of diseases of the liver. Unfortunately, the number of cases of cirrhosis is too small to permit one to arrive at a definite conclusion as to whether diminished function is a concomitant or an essential part of the disease.

TABLE 5.—*Observations on Patients with Miscellaneous Types of Hepatic Diseases*

Case	Sex and Age, Years	Enlargement of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm. 1 Hr.	2 Hr.	3 Hr.	4 Hr.	Total	Percentage of Normal	Comment
47	F. 38	0	8	0.15	0.20	0.43	0.63	1.41	47	Thrombocytopenic purpura; splenectomy; liver small and nodular
48	F. 59	0	0	0.10	0.25	0.33	0.42	1.10	37	Atrophic cirrhosis with ascites
				0.13	0.27	0.29	0.36	1.05	35	1 month later
49	M. 51	0	0	0.25	0.60	0.65	0.70	2.20	73	Atrophic cirrhosis with ascites
50	F. 51	++	0	0.38	0.47	0.52	0.55	1.92	64	Hypertrophic cirrhosis; tumor of pericardium; diarrhea
51	M. 68	++	0	0.23	0.66	0.76	0.71	2.36	79	Hypertrophic cirrhosis; diabetes; alcoholism
52	F. 49	++	0	0.33	0.67	0.79	0.65	2.44	81	Hypertrophic cirrhosis
53	F. 65	++	15	0.10	0.47	0.57	0.98	2.12	71	Recurrent jaundice; loss of weight; epigastric pain
54	M. 53	++	18	0.15	0.24	0.64	0.43	1.46	49	Syphilis; treated with bismuth and arsphenamine
55	F. 35	0	0	0.35	0.51	0.58	0.68	2.12	71	Toxemia of pregnancy
56	F. 45	++	20	0.13	0.70	0.60	0.72	2.15	72	Enlarged heart; septic temperature
57	M. 63	0	12	0.32	0.63	1.02	0.71	2.68	89	Transient jaundice postoperatively
58	F. 54	+	60	0.12	0.36	0.52	0.58	1.58	53	Diarrhea; brown pigmentationn of skin; achlorhydria
				0.17	0.30	0.27	0.23	0.97	32	1 month later

Nonhepatic Conditions.—In order to establish that the diminished production of hippuric acid is due only to damage to the liver, the test was carried out on a number of patients who had no clinical evidence of hepatic damage (table 6). It can readily be seen that in none of the patients was there a marked lowering of the production of hippuric acid. Two patients who had undergone nephrectomy (cases 30 and 74) showed a normal output. This indicates that one normal kidney can readily excrete hippuric acid as fast as it is produced. It should be mentioned that the kidneys' capacity to excrete hippuric acid is approxi-

3. Quick, A. J.: The Relationship Between Complement and Prothrombin, J. Immunol. **29**:87 (Aug.) 1935.

mately 50 per cent greater than the liver's ability to synthesize the compound. As a consequence, only in cases of severe damage to the kidneys does the test fail as a test of liver function because of renal retention of hippuric acid. Since no allowance was made for this margin

TABLE 6.—*Observations on Patients with Diseases Not Involving the Liver*

Case	Sex and Age, Years	Enlargement of Liver	Jaundice	Excretion of Hippuric Acid in Terms of Benzoic Acid, Gm. 1 Hr.	2 Hr.	3 Hr.	4 Hr.	Total	Percentage of Normal	Comment
59	M. 47	0	0	0.85	0.95	1.14	0.57	3.51	117	Chronic arthritis
60	F. 57	0	0	1.01	1.21	0.98	0.47	3.67	122	Chronic arthritis
61	F. 49	0	0	0.45	1.29	1.03	0.69	3.46	115	Chronic arthritis
62	M. 39	0	0	0.51	0.46	1.36	0.69	3.02	101	Chronic arthritis
63	F. 50	0	0	0.51	0.67	0.77	0.83	2.78	93	Chronic arthritis
64	M. 58	0	0	0.61	0.85	0.95	0.84	3.25	108	Chronic arthritis
65	M. 37	0	0	0.67	0.89	0.93	0.31	2.80	93	Diarrhea; possible infection with tropical disease; alcoholism
66	M. 41	0	0	0.94	1.22	0.93	0.27	3.36	112	Diarrhea; previous history of amebic dysentery
67	M. 62	0	0	0.33	0.78	0.93	0.80	2.84	95	Gastro-enteritis
68	M. 27	0	0	0.52	1.05	0.84	0.45	2.86	95	Gastric ulcer
69	M. 41	0	0	0.42	0.95	0.90	0.48	2.75	92	Gastric ulcer
70	M. 34	0	0	0.61	1.05	0.92	0.50	3.08	103	Gastric ulcer healed
71	F. 40	0	0	0.32	0.68	1.11	1.06	3.17	106	Pernicious anemia
72	F. 25	0	0	0.68	0.74	0.80	0.73	2.95	98	Secondary anemia of unknown cause
73	M. 33	+	0	0.50	1.04	0.88	0.55	2.97	98	Malaria
74	M. 35	0	0	0.48	0.80	0.92	0.96	3.16	105	Nephrectomy 2 weeks before
75	M. 32	0	0	....	0.93	1.04	1.09	3.06	102	Polycythemia
76	M. 49	+	0	0.25	1.07	1.10	0.98	3.40	113	Hodgkin's disease
77	F. 53	0	0	0.99	1.00	1.02	0.26	3.27	109	Multiple sclerosis
78	M. 24	0	0	0.72	0.85	0.91	0.62	3.10	103	Trichiniasis
79	F. 27	0	0	0.40	0.86	1.02	0.99	3.27	109	Post partum
80	M. 24	0	0	0.86	0.77	0.73	0.35	2.71	90	Neurosyphilis
81	M. 25	0	0	0.92	0.93	1.00	0.56	3.41	114	Alcoholism
82	M. 54	0	0	0.75	1.20	1.28	0.21	3.44	115	Diabetes, coronary disease
83	F. 83	0	0	0.27	0.63	0.85	0.67	2.41	81	Hypertensive heart disease
84	F. 67	0	0	0.62	0.82	0.88	0.63	2.95	98	Recurrent attacks of dyspnea; cyanosis
85	F. 70	+	0	0.19	1.06	0.80	0.88	2.93	98	Acute cardiac failure
86	F. 17	++	0	0.26	0.60	0.74	0.80	2.40	80	Rheumatic heart disease
87	M. 59	0	0	0.37	0.90	1.05	0.75	3.07	102	Essential hypertension
88	F. 52	0	0	0.78	0.75	1.10	1.27	3.90	130	Needle embedded in liver
89	M. 45	0	0	0.37	1.05	1.00	0.58	3.00	100	Excessive use of aminopyrine, acetophenetidin and other drugs
90	F. 47	0	0	0.30	0.54	0.90	0.74	2.48	83	Clinical picture suggested gout
91	M. 70	0	0	0.86	0.93	0.92	0.33	3.04	101	Moderate arteriosclerosis
92	M. 29	0	0	0.44	0.93	1.31	0.42	3.10	103	Deficiency disease
93	F. 54	0	0	0.35	0.64	0.85	1.04	2.88	96	Hypertension; dislocated shoulder
94	M. 47	0	0	0.26	0.80	0.92	0.74	2.72	91	Diabetes; alcoholism
95	M. 48	0	0	0.71	0.94	1.29	0.65	3.59	120	Neurasthenia
96	M. 42	0	0	0.72	1.30	0.52	0.44	2.98	99	Prostatic hypertrophy
97	M. 51	0	0	0.62	0.96	0.94	0.42	2.94	98	Hypothyroidism
98	M. 53	0	0	1.17	0.75	0.82	1.14	3.88	129	Hypothyroidism
99	F. 45	++	0	0.52	0.88	0.94	0.39	2.73	91	Cardiac failure; alcoholism
100	F. 65	0	0	0.76	1.26	0.68	0.59	3.29	110	Dermatitis (undiagnosed)

of reserve by the various investigators who attempted to utilize the synthesis of hippuric acid as a test of renal function, it is easy to understand why the test failed. Patients with an enlarged liver due to congestive heart failure gave results which were fairly well within normal

limits. Unfortunately, the present series contains no cases of hyperthyroidism, but a small number of patients studied by Shorr, Richardson and Wolff [4] gave normal results. Hirsheimer [5] has carried out the test on pregnant women and has observed that the production of hippuric acid declines up to the time of labor but immediately returns to normal after delivery. The cause of this is not known and requires further study. The output of hippuric acid has been normal in cases of myasthenia gravis [6] and of progressive muscular atrophy.[7]

COMMENT

Hepatic insufficiency can be determined only by a test specifically designed to estimate a physiologic function of the liver. The cardinal clinical signs of disease of the liver (change in the size and consistency of the organ and jaundice) are not per se evidence of hepatic insufficiency. The liver enlarged because of congestive heart failure may still exhibit normal function, while toxic hepatitis with no demonstrable change in the size of the liver may cause a severe decrease in function. Likewise, a patient with intense jaundice due to an obstruction caused by a stone of the common bile duct may have no appreciable disturbance of liver function, whereas another patient with low grade intrahepatic jaundice may show a marked degree of hepatic dysfunction. The need of a means for determining hepatic insufficiency is well recognized but does not appear to be met by the tests for liver function now in common use. There has been serious doubt whether any empirical test, such as the removal from the blood stream of a dye which is foreign to the body, can adequately serve as a criterion of the liver's efficiency, especially in view of the organ's multiplicity of functions.

A test based on the synthesis of hippuric acid should, however, yield a more accurate measure of the liver's ability to do its work. In the first place, the test determines an important function, namely, that of detoxication. Probably the mechanism that combines benzoic acid with animo-acetic acid is the same as that which unites cholic acid to amino-acetic acid to form glycocholic acid, one of the important acids of bile. In the second place, the test depends on the liver's capacity to synthesize

4. Shorr, E.; Richardson, H. B., and Wolff, H. G.: Endogenous Glycine Formation in Myopathies and Graves' Disease, Proc. Soc. Exper. Biol. & Med. **31**:207 (Nov.) 1933.

5. Hirsheimer, A.: Personal communication to the author.

6. Quick.[2] Shorr, Richardson and Wolff.[4]

7. Freiber, I. K., and West, E. S.: Glycine Synthesis in Pseudohypertrophic Dystrophy, J. Biol. Chem. **101**:449 (July) 1933. Linneweh, W., and Linneweh, F.: Zur Frage des Glykokollmangels und der Glykokolltherapie bei progressiver Muskeldystrophie, Deutsches Arch. f. klin. Med. **176**:526, 1934.

amino-acetic acid. With the increasing realization of the probable importance of amino-acetic acid in physiology of the muscles and perhaps even in other metabolic processes, any test furnishing information concerning the body's capacity to produce amino-acetic acid should become clinically useful. The test for hippuric acid depending thus on two important functions of the liver should give a truer evaluation of hepatic insufficiency than an empirical test. The high incidence of diminished production of hippuric acid, especially in cases of chronic hepatic diseases, can be considered as confirmatory evidence. The test for hippuric acid offers the distinct advantage that it gives results which seem to correspond fairly closely to the clinical picture and, according to Vaccaro, to the gross pathologic process.

Much of the clinical research on function of the liver has had for its object finding a test which would aid in differential diagnosis. There is a distinct need for distinguishing between an obstructive type of jaundice, which often requires surgical intervention, and intrahepatic jaundice, which must be treated medically. Not infrequently to make an accurate diagnosis is exceedingly difficult, and although laboratory tests are not infallible, they are often helpful. From the series of cases presented in this paper it can be seen that the test for hippuric acid gives low results in cases of catarrhal jaundice, acute and chronic hepatitis, usually in cases of a malignant process with metastasis to the liver and in cases of hypertrophic and atrophic cirrhosis and, from earlier studies, syphilitic cirrhosis. Normal results are obtained in cases of uncomplicated cholecystitis and cholelithiasis, including obstruction due to stones in the common duct. The test therefore is valuable in differentiating between toxic or intrahepatic jaundice and jaundice arising from an obstruction due to a stone in the common duct. Certain difficulties, however, cannot be ignored. An obstruction of the common duct of long duration may ultimately bring about damage to the liver demonstrable both histologically and functionally. Significantly, obstruction due to a malignant process, especially one of the head of the pancreas, will cause a definite diminution of the output of hippuric acid and often also a positive reaction to the test for galactose, as Banks, Sprague, and Snell [8] have observed. No differentiation between toxic jaundice and one produced by an obstruction from a malignant growth can be made with certainty on tests of function alone. Neither the test for hippuric acid nor any other test can or should be made the sole basis for making a diagnosis. The proper correlation of the clinical history with the physical findings and the results of a test for function, such as one for the synthesis of hippuric acid, are necessary for arriv-

8. Banks, B. M.; Sprague, P. H., and Snell, A. M.: Clinical Evaluation of the Galactose Tolerance Test, J. A. M. A. **100**:1987 (June 24) 1933

ing at a reasonably correct diagnosis. Every case of jaundice can be profitably studied by the test for hippuric acid, especially if surgical treatment is considered. If the test shows an output below 65 per cent of normal, the possibility of toxic jaundice should be carefully considered.

Usually little difficulty is encountered in differentiating between enlargement of the liver due to congestive heart failure and that due to chronic hepatitis. Nevertheless, there is always the danger of overlooking or mistaking chronic hepatitis for congestion of the liver when signs of cardiac involvement are present. Since the test for hippuric acid gives low results in cases of hepatitis and yields normal figures in cases of uncomplicated cardiac congestion, the test often proves useful.

The test for hippuric acid has definite prognostic value. While it presumably measures hepatic impairment, a low result does not necessarily mean a fatal outcome. The patient in whom severe hepatitis developed from carbon tetra-chloride (case 11) had an output of only 17 per cent, but with prompt treatment the output was restored to nearly normal in six weeks. The test is most useful when repeated to follow the course of the disease. In cases of catarrhal jaundice and acute hepatitis the production of hippuric acid returns to normal as the clinical condition improves. The test is useful in evaluating therapy, and evidence indicates that patients with catarrhal jaundice and various forms of hepatitis can be benefited by a routine treatment which will be discussed later. Certain patients with damage to the liver, however, seem highly refractive to treatment. Thus, the patient in case 48, who had atrophic cirrhosis with ascites, showed no improvement either clinically or according to the test for hippuric acid after intensive treatment for one month.

It is desirable that a test for function contribute toward a broader understanding of the physiology of the organ the efficiency of which it is intended to measure. One of the important functions attributed to the liver is that of detoxication, yet the present knowledge concerning this subject is meager and unsatisfactory. The synthesis of hippuric acid offers one of the easiest and most available means for studying the mechanism of detoxication. Of particular interest is the observation that sodium benzoate consistently depresses the excretion of uric acid. In various types of hepatic injury the retention of uric acid due to sodium benzoate may become very pronounced, as I have recently reported.[9] Such observations clearly indicate that the retention of uric

9. Quick, A. J.: A New Concept of the Significance of Uric Acid in Clinical Medicine, M. Clin. North America **17**:1325 (March) 1934; The Effect of Exercise on the Excretion of Uric Acid with a Note on the Influence of Benzoic Acid on Uric Elimination in Liver Diseases, J. Biol. Chem. **110**:107 (June) 1935.

acid may occur in the absence of renal disease and furthermore that the liver undoubtedly plays an important rôle in uric acid metabolism. Further investigation concerning the relationship between dysfunction of the liver and retention of uric acid should yield valuable results.

It is not my purpose in this paper to compare the test for hippuric acid with other methods. Nevertheless, some of its advantages should be pointed out. The test does not require intravenous injection; its simplicity makes it available to those who possess only meager laboratory equipment, and it subjects the patient to very little inconvenience. Sodium benzoate, moreover, is a relatively harmless drug, which can be given in the presence of severe hepatic damage without danger of causing further injury or producing serious toxic effects. In fact, the therapeutic doses employed by such clinicians as Senator [10] were larger than the dose used in this test. It should be mentioned that the test is very inexpensive, which strongly recommends it as a routine procedure. The high cost of galactose is a serious obstacle to the wide use of Bauer's test.

TREATMENT

The patient with hepatic involvement can often be benefited by proper therapeutic measures. Of greatest importance is the diet. A diet high in carbohydrate has long been regarded as beneficial in cases of hepatic damage. Recently Althausen [11] thoroughly discussed the use of dextrose. Intravenous injection of dextrose seems to be indicated only when it is difficult or impossible to give it orally. If the patient has an intolerance for fat, its intake should be restricted. Often, however, in cases of chronic disease the tolerance can be appreciably increased by the administration of bile salts. Proteins should be supplied mainly in the form of milk. Meat, soup, broth and other meat extracts should not be given, since Bollman and Mann [12] have obtained experimental evidence that meat extracts are distinctly deleterious when hepatic damage exists. It is also well known that meat is badly tolerated by dogs with an Eck fistula. A liberal supply of the antineuritic vitamin should be provided. Vitamin D is also important, because of its relation to calcium metabolism, and is best given in the form of viosterol. Calcium often is very effective in the treatment of acute hepatitis and seems beneficial also in cases of the more chronic type. In cases of acute involvement 10 cc. of a 10 per cent solution of calcium gluconate should be administered intravenously daily for from three to four days

10. Senator, H.: Ueber die Wirkung der Benzoesaure bei der rheumatischen Polyarthritis, Ztschr. f. klin. Med. **1**:243, 1879.

11. Althausen, T. L.: Dextrose Therapy in Diseases of the Liver, J. A. M. A. **100**:1163 (April 15) 1933.

12. Bollman, J. L., and Mann, F. C.: Experimentally Produced Lesions of the Liver, Ann. Int. Med. **5**:699 (Dec.) 1931.

and then from 5 to 10 Gm. orally. In chronic cases calcium need be given only orally. The patient should be given 5 Gm. of gelatin three times a day. It is best to mix the dry granular gelatin with a little fruit juice just before administering it. Gelatin is rich in amino-acetic acid, which is an important amino-acid that presumably is synthesized mainly by the liver. Since other proteins are relatively poor in amino-acetic acid and since the damaged liver may have an impairment of its synthetic power, it seems logical to supply amino-acetic acid, and this is most economically done with gelatin, which contains 25 per cent of the acid. Furthermore, gelatin is free from the aromatic amino-acids which in instances of intestinal putrefaction are converted to toxic amines and phenols. These are particularly dangerous when the detoxifying function of the liver is diminished.

SUMMARY

The excretion of hippuric acid after the administration of sodium benzoate was studied in a series of one hundred cases, in fifty-eight of which hepatic or biliary disease was present. A patient with a normally functioning liver excretes approximately 3 Gm. of benzoic acid in the form of hippuric acid in four hours after taking 6 Gm. of sodium benzoate. A low output of hippuric acid occurs in cases of catarrhal jaundice and various forms of hepatitis and usually in cases of a malignant process with metastasis to the liver, syphilitic cirrhosis and atrophic and hypertrophic cirrhosis. Reaction to the test is normal in cases of cholecystitis, cholelithiasis and biliary obstruction due to stones in the common duct if the condition is of short duration. The test appears as a promising means for estimating hepatic insufficiency and as an aid in the differential diagnosis, especially in distinguishing between the jaundice of hepatitis and the jaundice arising from obstruction due to a stone in the common duct. The test is useful in following the course of disease of the liver and in determining the effectiveness of therapy. A routine for the treatment of patients with damage to the liver has been outlined.

THE HEREDITARY FACTOR IN OBESITY

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Definite progress in the treatment of obesity has been made in recent years. Studies in water balance, a better understanding of the glands of internal secretion and their function, a more intelligent conception of dietary requirements and, finally, the pressure of modern fashion, which sends so many stout women to the physician, have all made important contributions to this progress. Yet, when one attempts to classify many cases of obesity, either on an etiologic or on a clinical basis, confusion and uncertainty remain. As early as 1910 Lyon [1] clearly indicated this difficulty, and Jarlov,[2] in his exhaustive work, well illustrated the disagreement and difficulties in classification, even when the etiology was entirely disregarded. If etiology is considered, there is even more confusion. The arguments for endogenous obesity versus exogenous obesity are familiar.[3] The appetite theory, the relationship of occupation to obesity and the depression of metabolism [4] and the dynamic action of food stuff [5] as causes for stoutness have all been studied thoroughly. No one cause by itself explains obesity. However, in this maze of conflicting conceptions and findings, four facts seem to stand out clearly: 1. Obese persons lose weight on a restricted caloric intake. 2. Obesity occurs in patients with hypopituitarism. 3. Obesity occurs in patients with hypothyroidism. 4. Heredity plays more than a coincidental part. To this last fact this discussion will be confined.

That heredity is an important factor in obesity is recognized by most workers in this field. However, it is questionable whether it has

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1. Lyon, I. P.: Adiposis and Lipomatosis, Arch. Int. Med. **6**:28 (July) 1910.

2. Jarlov, E.: The Clinical Types of Abnormal Obesity, Acta med. Scandinav., supp. 42, 1932, p. 5.

3. Newburgh, L. H., and Johnston, M. W.: Endogenous Obesity: A Misconception, Ann. Int. Med. **3**:815 (Feb.) 1930. Eidelsberger, Joseph: Obesity with Special Reference to Endocrinopathic Origin, Ann. Int. Med. **3**:604 (Dec.) 1929.

4. Silver, S., and Bauer, J.: Obesity, Constitutional or Endocrine, Am. J. M. Sc. **181**:769 (June) 1931.

5. Bowen, B. D.; Griffith, F. R., Jr., and Sly, G. E.: The Effect of a High Fat Meal on the Respiratory Quotient and Heat Production of Normal and Obese Individuals, J. Nutrition **8**:432, 1934.

received sufficient emphasis in medical discussions. The findings of Davenport [6] seem definitely to indicate that body build follows the mendelian laws of inheritance. By studying the progeny of parents of similar and dissimilar builds, he concluded that there are three gametic factors, of which one may correspond to dystrophy of the thyroid, and one to dystrophy of the pituitary and the third may be a metabolic factor that affects the actual metabolism of the cells themselves. If this hereditary factor is accepted, the onset of obesity in one person as opposed to that in another who is subject to the same environmental influences and is even receiving the same diet may be more readily understood.

Seventy-five stout women were studied in the outpatient department of the Buffalo General Hospital with three points in mind: (1) the factors associated with the onset of obesity as compared with the same factors occurring in a nonstout control group; (2) the incidence of obesity in the parents of the stout group as opposed to that in the parents of the nonstout control group; (3) the body build of the progeny of different matings with special reference to mendelian inheritance of build.

Who is stout and who is merely heavyset is an important and difficult question. I interviewed each patient individually and chose only those who were unquestionably stout for this study. Davenport's [6] figures for age and height were used as standards, each patient being over 15 pounds (6.8 Kg.) heavier than the average for her particular age and height. Originally, the patients in the stout group were subdivided, according to their weight, into stout and excessively stout groups, but as the findings were approximately the same in those two groups, they have been combined as merely the stout group for purposes of simplification. In many cases the statement of the patient had to be taken as to the build of the members of her family, introducing, of course, a definite source of error. However, when there was any reasonable doubt, that history was discarded.

Fifty-five women who were definitely not stout were chosen at random as controls. Patients with any debilitating illness were not included. The control patients came from approximately the same age group and had approximately the same incidence of operations and pregnancies—the two most common factors apparently associated with the onset of obesity (tables 1 and 2).

Eighty-three per cent of the stout group were between 21 and 50 years of age, which includes the period of childbearing and the menopause. Eighty-six per cent of the nonstout group were in this same age period. Sixty-one per cent of the stout group and 50 per cent

6. Davenport, C. B.: Body-Build and Its Inheritance, Washington, D. C., Carnegie Institution of Washington, 1923.

of the control group had had one or more pregnancies. Thirty-six per cent of the stout group and 47 per cent of the nonstout group had had operations. Thus the two groups may be compared, being from approximately the same age period and having had approximately the same number of pregnancies and operations.

Sixty-three women in the stout group gave a reliable history as to the onset of obesity. Of the 41 of these who bore children, or 65 per cent, 29, or 71 per cent, stated a direct association between pregnancy and the onset of obesity. Of the 24 who had major operations, or 38 per cent, 7, or 29 per cent, stated a direct association between the operation and the onset of obesity. Of the remaining 27 patients, 4 associated the onset of obesity with puberty and 2 with the menopause, 8 maintained they were "always stout" and 13 apparently had no determinable factor associated with the onset of obesity. Thus, in

TABLE 1.—*Age Distribution of Stout and Control Groups*

	Decade					
	Second	Third	Fourth	Fifth	Sixth	Seventh
Stout	6	15	21	24	4	2
Nonstout	1	19	17	8	5	1

TABLE 2.—*Causes of the Onset of Obesity in Women*

Pregnancy	Operation	Puberty	Menopause	"Always Stout"	Miscellaneous Causes
29	7	4	2	8	13

67 per cent of the stout group, the onset of obesity was apparently associated with some physiologic or physical episode. However, in another group of women of approximately the same age period and subject to the same physiologic and physical episodes, obesity did not occur.

When one studies the builds of the parents of the stout and the control group a very definite and real difference in the incidence of obesity is apparent (table 3). Of the 61 stout women whose family history seemed unquestionably reliable, 26, or 43 per cent, had a stout mother; 9, or 15 per cent, had a stout father, and 15, or 25 per cent, had both a stout mother and a stout father, making a total of 50, or 82 per cent, having either one or both parents stout. In contrast to this, of the 47 nonstout patients with an equally reliable family history, 14, or 30 per cent, had a stout mother; 1, or 2 per cent, had a stout father, and 3, or 6 per cent, had both a stout mother and a stout father, making a total of 18, or 38 per cent, with either one or both parents stout, as opposed to 82 per cent in the stout group.

If build is inherited, as it seems to be from these figures, this inheritance must be along mendelian lines, as there is probably no other kind of inheritance.[7] A study of inheritance in human beings is, of course, exceedingly difficult because so few generations are available for observation. However, if segregation, which is the indispensable condition of the mendelian theory, can be shown, it follows inescapably that mendelian inheritance is present. Segregation is the dissociation of two unit characters from each other in the course of the formation of the germ cells. Thus, evidence for segregation in human inheritance is a difference in variability of the progeny of different matings.[6]

A study of the progeny of different matings in this group shows a definite difference in variability (table 4). There were 89 offspring from matings of stout persons, 65, or 73 per cent, of whom were stout,

TABLE 3.—*Incidence of Obesity in the Parents of Patients in the Stout and in the Control Group*

Group	Mother Stout	Father Stout	Mother and Father Stout	Mother and Father Nonstout
Stout	26	9	15	11
Nonstout	14	1	3	29

TABLE 4.—*Data on the Variability of the Progeny of Different Matings*

Matings	Stout Progeny	Nonstout Progeny
Stout and stout	65	24
Stout and nonstout	70	100
Nonstout and nonstout	16	160

and 24, or 27 per cent, of whom were not stout. Of the 170 offspring of matings of a stout and a nonstout person, 70, or 41 per cent, were stout, and 100, or 59 per cent, were not stout—a marked variability. Of the 176 offspring of matings of nonstout persons, only 16, or 9 per cent, were stout, in contrast to the 160, or 91 per cent, who were not stout. Thus, there is present a marked difference in variability in the progeny of different matings, with the offspring of a stout and a nonstout parent the most variable and the offspring of nonstout parents the least variable. The fact that the offspring of stout parents are more variable than those of nonstout parents suggests, as pointed out by Davenport, that stout persons carry gametes for slenderness whereas nonstout persons rarely carry gametes for stoutness. As a corollary to this, regression to a more normal build as a result of these gametes for

7. Conklin, E. G.: Heredity and Environment, ed. 3, Princeton, N. J., Princeton University Press, 1920, p. 107.

slenderness can be seen in the offspring of stout parents to a considerably greater degree than in the offspring of slender parents.

There appears to be no definite dominance in the series, which, of course, is not essential in mendelian inheritance.

CONCLUSIONS

Pregnancy or a major operative procedure appeared to be the most common factor associated with the onset of obesity in a group of 63 stout women.

Obesity did not develop in another group of women from approximately the same age group and with approximately the same incidence of pregnancies and operations.

The incidence of obesity in the parents of the stout group was markedly greater than in the parents of a group of nonstout women.

A study of the progeny of different parents indicates segregation, which is evidence for mendelian inheritance of build.

It is suggested that consideration of the hereditary factor in obesity may help to explain the apparent inconsistency of build in persons subject to the same environmental influences.

RECOVERY FROM GENERALIZED AMYLOIDOSIS SECONDARY TO PULMONARY TUBERCULOSIS

REPORT OF A CASE

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Recovery from amyloidosis in a patient with chronic progressive pulmonary tuberculosis is a clinical curiosity. While it is true that experimentation with animals [1] and clinical observations [2] have repeatedly demonstrated that amyloid tissue can undergo spontaneous absorption if the causative agent is removed, unfortunately the tuberculous patient with amyloidosis rarely recovers from the primary process. The following is a report of a case of clinical cure of generalized amyloidosis secondary to extensive pulmonary tuberculosis and tuberculous pyothorax. The patient has been under my observation for the past four years, during which time the entire cycle of development and regression of the amyloid process has been carefully followed.

REPORT OF CASE

A. K., a 34 year old man, was admitted to the country sanatorium of the Montefiore Hospital in August 1931, with a history of a productive cough and fever of five months' duration. Examination disclosed a fibrocaseous infiltration of the entire right lung, with a large cavity in the hilar region and an exudative infiltration in the midzonal portion of the left lung. The sputum contained tubercle bacilli. The temperature ranged between 100 and 102 F. Pneumothorax was induced on the right side and was continued effectively for two and a half months, at the end of which time an effusion occurred. Examination of the fluid showed it to be purulent, with many tubercle bacilli and gram-positive cocci and bacilli. Pneumothorax was discontinued and was replaced by aspiration of the pus, but the condition was progressive, and in January 1932 an empyema necessitatis perforated through the eighth intercostal space in the midscapular line.

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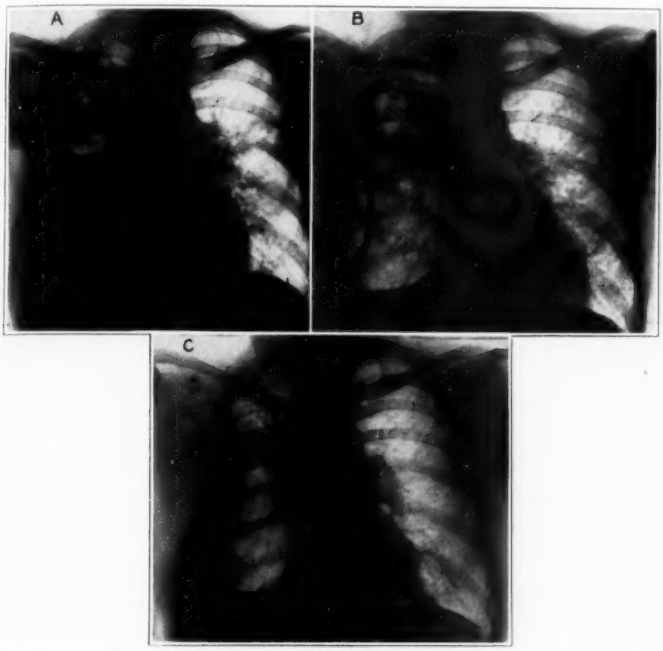
* Sigmund M. Lehman Fellow.

From the tuberculosis division of the Montefiore Hospital.

1. Kuczynski, M. H.: Neue Beiträge zur Lehre vom Amyloid, Klin. Wchnschr. **2**:727 (April 16) 1923; Weitere Beiträge zur Lehre vom Amyloid, ibid. **2**:2193 (Nov. 26) 1923.

2. Fagge, C.: The Principles and Practice of Medicine, Philadelphia, P. Blakiston's Son & Co., 1886, vol. 2, p. 489. Gairdner, W., in discussion on Delafield, F.: Diseases of the Kidneys, Tr. A. Am. Physicians **6**:149, 1891. Herringham, W. P.: Kidney Diseases, New York, Oxford University Press, 1912, p. 353. Walker, G. F.: Case of Recovery from Amyloid Disease, Lancet **2**:120 (July 21) 1928.

The patient was transferred to the city institution in March 1932, in a very toxic condition, with the temperature fluctuating between 99 and 104 F. Roentgenograms showed the effusion to be at the level of the seventh rib in the midaxillary line, with a small area of pneumothorax above the line of the fluid. In the left lung there were visualized many small cavities in the upper lobe and discrete tubercles scattered throughout the lower lobe. Treatment consisted of aspirations of from 400 to 800 cc. of pus twice weekly, followed by the instillation of a 10 per cent concentration of a cajaput oil (from Melaleuca viridiflora). No improvement was noted with respect to either the local or the constitutional manifestations.



A. Roentgenogram of the chest showing pyopneumothorax of the right lung and extensive fibrocaseous cavitary involvement of the left lung on May 16, 1932. *B*. On Dec. 28, 1932, the thoracotomy tube had completely drained the right pleural cavity; the pleura was thickened, and parenchymal lesions were visualized. There was an increase of infiltrations in the lower lobe of the left lung. *C*. On Oct. 18, 1935, the fluid in the right side of the chest had been drained completely. The roentgenogram shows marked evidence of absorption and fibrosis in the upper lobe of the right lung and considerable clearing in the left lung.

On May 20, 1932, a simple thoracotomy was done with the area under local anesthesia, and a rubber catheter was inserted in the seventh interspace in the posterior axillary line. About a gallon (3.8 liters) of pus was removed at the time of operation, and subsequently there was free drainage through the tube.

The fever persisted for several weeks, but by July a definite improvement was noted, which has continued up to the present time. In January 1933 the patient became afebrile, and since August 1933 the results of examination of the sputum have all been negative. He was discharged from the hospital in August 1934 and has since been followed in the outpatient department. At the time of writing (May 1935) there is drainage of about 0.5 cc. of pus daily through the sinus of the thoracotomy wound, the tube having been removed two years before. His general condition is excellent, and since the operation he has gained over 50 pounds (22 Kg.) in weight. Serial roentgenograms (illustration) showed complete absorption of the fluid from the right side of the chest and marked improvement of the condition in the left lung.

COMMENT

The lengthy period of observation of this patient (almost four years) has enabled me to study accurately both the onset and the regression of the amyloid changes. The table depicts the course of the entire amyloid process in terms of retention of congo red, physical signs and findings in the blood and urine.

Clinical Manifestations of Amyloid Progression and Regression

Date	Retention of Congo Red, Percentage	Hepatomegaly	Splenomegaly	Edema	Albumin in Urine (Gm. Daily)	Serum Proteins (Gm. per 100 Cc.)		Urea Nitrogen
						Albumin	Globulin	
7/32	54	+	0	0	5	2.96	2.36	11.2
10/32	90	++	+	+	9	1.96	2.36	....
2/33	100	+++	++	++	10	1.97	2.17	....
8/33	75	+++	++	++	7	2.90	1.76	14.4
7/34	45	+++	+	++	2	....	....	....
11/34	28	++	+	+	2	....	....	....
1/35	..	+	0	+	2	3.22	3.48	15.6
4/35	10	0	0	0	1.75	....	....	....

Study of the table brings forth many interesting points. First, healing of the tuberculous disease did not immediately initiate regression of the amyloid process. As a matter of fact, progression was most marked during the last six months of 1932, at the time that the pathologic condition of the lungs and the constitutional symptoms were showing marked improvement. The first test with congo red, in July 1932, showed 54 per cent retention in the tissues, just enough to enable a positive diagnosis of amyloidosis to be made, and at that time the only significant clinical finding was albuminuria. Four months later, despite the improvement in the tuberculous condition, there was almost complete retention of the dye (90 per cent), and both the liver and the spleen were palpable. In addition, there were peripheral edema and other associated manifestations of the nephrotic syndrome indicating extensive renal involvement.[3] From August 1933 to the present the retention of congo red diminished steadily until at the last deter-

3. Rosenblatt, M. B.: Clinical Manifestations of Amyloidosis, Ann. Int. Med. **8**:678 (Dec.) 1934.

nation, in April 1935, the reading was only 10 per cent. It is to be noted that in November 1934, when the retention was 28 per cent, a figure within the normal range, hepatomegaly, splenomegaly and edema were still observed. At the time of writing the only clinical finding is albuminuria, which is relatively slight. The proteins of the blood serum have been completely restored. Despite the clinical evidence of extensive renal involvement for three years, there has been no impairment of renal function at any time.

During the last year of his hospitalization the patient was given liver therapy, but it is felt that the regression of the amyloidosis could be more properly attributed to the improvement in the tuberculosis than to the effects of the specific treatment.

FURTHER DATA ON ARTIFICIAL PNEUMOTHORAX IN EXPERIMENTAL LOBAR PNEUMONIA

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The optimistic reports of numerous foreign clinicians on the use of therapeutic pneumothorax in cases of lobar pneumonia and the encouraging results obtained by us in our first experimental study on dogs[1] have prompted a number of American physicians to resort to artificial pneumothorax in the treatment of lobar pneumonia. The present clinical status of this procedure has recently been presented.[2] No further experimental work on animals has been published, and no studies on patients have been made in an effort to explain the modus operandi of this treatment, except those of Blake, Howard and Hull.[3]

These authors studied the agglutinins of the serum of twenty-two patients and found that "agglutinins apparently appear in the blood just about the same as they do in the untreated cases." This is significant, because in some of the cases clinical recovery as judged by the usual criteria occurred as early as six days before there was an appreciable response of the antibodies.

During the past year we have pursued three lines of investigation, hoping by these means to shed light on the reasons for the clinical phenomena frequently observed when artificial pneumothorax is employed in the treatment of lobar pneumonia, both in the experimental animal and in man.

From the Thoracic Section of the Medical Division, the Hospital of the University of Pennsylvania.

Read before the Section on Practice of Medicine at the Joint Session of the American Medical Association and the Canadian Medical Association, Atlantic City, N. J., June 12, 1935.

The experimental work was concluded in the Laboratories of Bacteriology and Surgical Research of the University of Pennsylvania School of Medicine. The study was aided by a grant from the Faculty Research Committee of the University of Pennsylvania.

1. Lieberman, L. M., and Leopold, S. S.: Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs, Am. J. M. Sc. **187**:315 (March) 1934.

2. Leopold, S. S., and Lieberman, L. M.: The Present Status of Artificial Pneumothorax in the Treatment of Lobar Pneumonia, Ann. Int. Med. **9**:19 (July) 1935.

3. Blake, F. G.; Howard, M. E., and Hull, W. S.: The Treatment of Lobar Pneumonia by Artificial Pneumothorax, Tr. A. Am. Physicians **49**:119, 1934.

This presentation is concerned with the following problems: (*a*) the time of appearance of specific antibodies in the blood of dogs in which lobar pneumonia was induced, both those not treated and those treated with artificial pneumothorax; (*b*) the effect of pneumothorax on lymphatic drainage in the lungs of uninfected rats, and (*c*) the effect of artificial pneumothorax on experimental bacteremia in dogs induced by the pneumococcus.

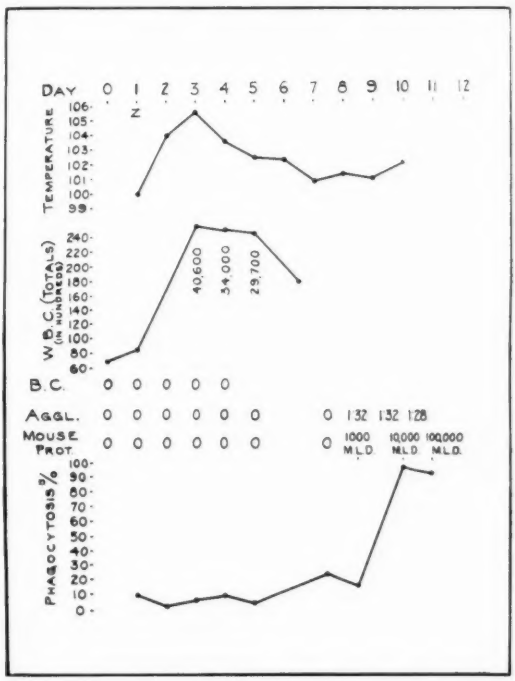

Fig. 1 (dog 667B).—Temperatures, leukocyte counts, blood cultures (*B.C.*) and results of serum agglutination (*AGGL*), mouse protection and phagocytosis tests during experimental lobar pneumonia induced in an untreated dog. In this chart *z* marks the time of injection.

TIME OF APPEARANCE OF SPECIFIC ANTIBODIES IN BLOOD OF DOGS WITH LOBAR PNEUMONIA, BOTH THOSE NOT TREATED AND THOSE TREATED WITH ARTIFICIAL PNEUMOTHORAX

In collaboration with the laboratory of bacteriology, we produced lobar pneumonia in dogs with type I pneumococcus by a modified Robertson technic.[1] In addition to the usual clinical observations, cultures of the blood, determinations of serum agglutination, mouse protection tests and estimations of the phagocytic

power of whole blood were made. The last test was carried out by the method recently described by Boerner and Mudd.[4] In brief it is performed as follows: Venous blood is added to purified heparin and placed in an agitator bath kept at a temperature of between 37 and 38 C. To this is added the suspension of bacteria. At intervals of three minutes sufficient blood is removed by a capillary pipet, without stopping the agitator, to make the usual blood smears. These are fixed and stained by the Giemsa method. The results are expressed in terms of the percentages of positive cells, i. e., those which show bacteria within the cytoplasm. Curves are obtained by plotting the percentage of positive cells against the time intervals. Our curves are those obtained after fifteen minutes. It was

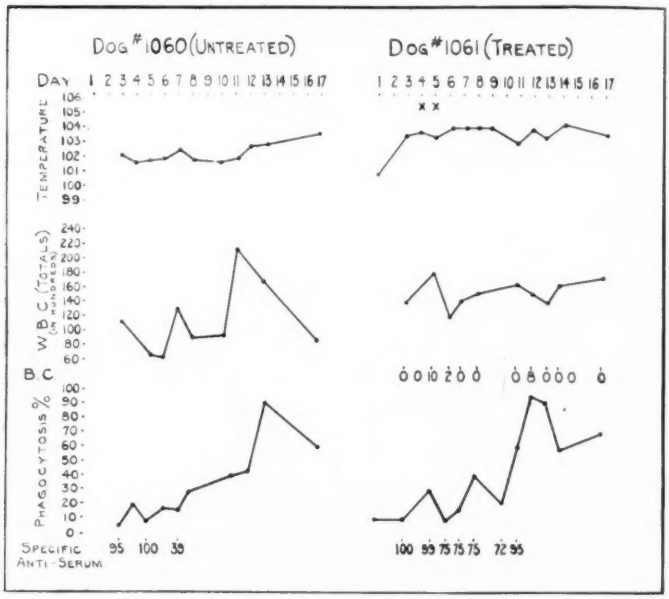

Fig. 2.—Temperatures, leukocyte counts, blood cultures (*B.C.*) and results of the phagocytosis tests during experimental lobar pneumonia induced in an untreated dog and in one treated (dog 1,061) with artificial pneumothorax. In this chart and in the graph shown in figure 3, *x* indicates the time at which pneumothorax was given.

soon ascertained that, while the results of the phagocytosis test corresponded with those of the mouse protection test and with those of the determinations of agglutinins, it was more delicate than either. The results of the latter tests were therefore discarded in favor of the estimations of phagocytosis.

4. Boerner, F., and Mudd, S.: Determination of Phagocytic Power of Whole Blood or Plasma-Leukocyte Mixtures for Clinical or Experimental Purposes; Description of an Improved Method with Representative Findings, Am. J. M. Sc. **189**:22, 1935.

Untreated animals were studied first, and it was found that usually before infection and for the first few days thereafter the amount of phagocytosis-promoting antibodies was negligible and that for the next few days it remained well below 50 per cent. Thereafter, the percentage gradually increased, and between the tenth and the fourteenth day it rose abruptly to nearly 100 per cent and remained there. Treatment with artificial pneumothorax did not alter the phagocytic power of the animal's whole blood. In order to check the test for both the untreated and the treated animals, specific type I antipneumococcus serum in a dilution of 1:50 was added to otherwise similarly prepared tubes. With the exception of a single low value these tubes showed marked phagocytosis (from 72 to 100 per cent).

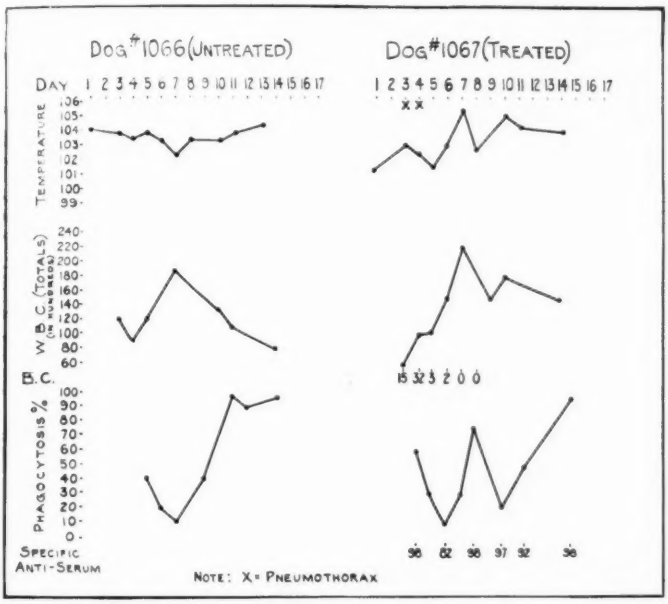

Fig. 3.—Temperatures, leukocyte counts, blood cultures (*B.C.*) and results of the phagocytosis tests during experimental lobar pneumonia in an untreated dog and in one treated with artificial pneumothorax.

EFFECT OF ARTIFICIAL PNEUMOTHORAX ON LYMPHATIC DRAINAGE IN LUNGS OF UNINFECTED RATS

Dr. Henry Hopkins, of the clinic for thoracic diseases, and Dr. John Griffith, of the Robinette Foundation of the Hospital of the University of Pennsylvania, have studied the effect of artificial pneumothorax on the lymphatic drainage in the lungs of uninfected rats. Thorium dioxide was injected through the wall of the chest into the parenchyma of each lung near the base, the symmetry of the injections being checked by roentgenograms. One lung was then collapsed. The spread of thorium dioxide was observed by a series of roentgenograms. After

considerable time this substance was rejected because of technical difficulties, and at present other roentgenographically opaque substances are used which appear to have a slower rate of spread. With the use of suspensions of carbon it has been possible to show a decrease in the amount and the extent of the spread, both grossly and microscopically, in the collapsed lung. The regional lymph nodes also showed a distinct difference between the two sides. In the expanded lung the lymphatics of the parietal pleura and the diaphragm showed considerable carbon, whereas there was little on the side of the collapsed lung.

Although the work is still incomplete, there is evidence to show that pneumothorax definitely decreases the amount and the rate of spread of foreign material from the collapsed lung to the adjacent lymphatics. Similar observations have been reported by Shingu,[5] who exposed rabbits to atmospheres of soot before and after producing artificial pneumothorax, and by White and Gammon,[6] who injected oil colored with sudan into the jugular veins of experimental animals and then studied the distribution of pigment in the collapsed and in the fully expanded lungs. There is, therefore, considerable evidence that particulate matter is retained in the compressed lung, its absorption being retarded by obstruction of the lymphatic vessels. Similarly, it is conceivable that the good effects of compression therapy in the early stages of clinical and experimental lobar pneumonia may be due to the retardation of the dissemination of toxic products or bacteria, or both, from the diseased lung to the adjacent lymphatics.

EFFECT OF ARTIFICIAL PNEUMOTHORAX ON EXPERIMENTAL BACTEREMIA IN DOGS INDUCED BY PNEUMOCOCCUS

We were encouraged to pursue this study because in our first publication we reported on one animal (dog 1,023) which was treated and recovered, despite an overwhelming invasion of the blood stream. In this connection, it is of interest that Robertson and his associates,[7] who produced experimental lobar pneumonia with Pneumococcus in more than one hundred dogs, all untreated, stated that only one dog with a blood culture showing more than 50 colonies per cubic centimeter recovered.

In an effort to determine the proper dosage of pneumococci for inoculation varying amounts of culture were used in order to obtain the greatest number of

5. Shingu, Susuo: Beitrag zur Physiologie des künstlichen Pneumothorax und seiner Wirkung auf die Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **11**:1, 1908.

6. White, W. C., and Gammon, A. M.: Some New Features of Interest About the Pulmonary Circulation and the Fate Therein of Intravenously Introduced Fats, Tr. Nat. A. Prev. Tuberc. **10**:215, 1914.

7. Terrell, E. T.; Robertson, O. H., and Coggeshall, L. T.: Experimental Pneumococcic Lobar Pneumonia in the Dog: Method of Production and Course of the Disease, J. Clin. Investigation **12**:393, 1933.

positive blood cultures compatible with the continuation of life for at least forty-eight hours. With injection of 0.1 cc. of sedimented pneumococci of type I bacteremia developed in 70 per cent of the dogs; with 0.125 cc. the incidence was 75 per cent; with 0.2 cc., 92 per cent, and with 0.25 cc. and 0.3 cc., 100 per cent.

In our previous work, with the use of 0.06 cc. of sedimented pneumococci of type I or type III, six of eighteen treated dogs had bacteremia. All these animals, including dog 1,023, with a blood culture containing an uncountable number of colonies, recovered. Of the group of eighteen untreated dogs used as controls, eight showed bacteremia during life, and only one recovered. Pneumococci were noted post mortem in the blood of the hearts of two others. The results in the two groups cannot be compared, because six of the nine dogs with bacteremia

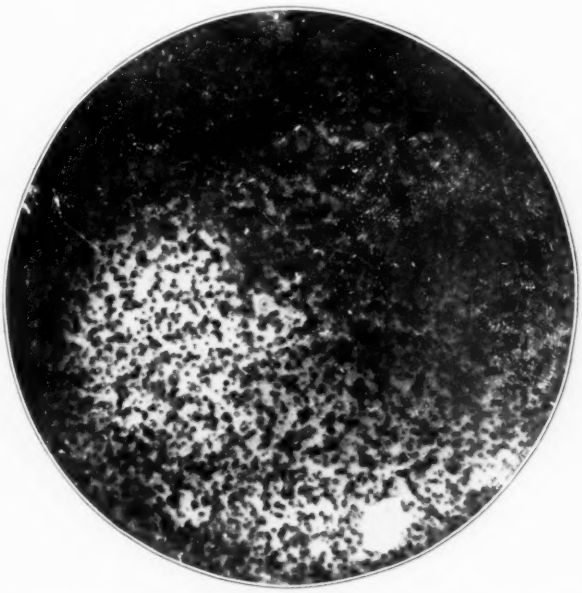

Fig. 4 (dog 523).—Colonies obtained from 1 cc. of the blood culture on the second day of the disease before the first treatment. Death occurred on the sixth day.

which died succumbed within forty-eight hours and therefore could not have been given pneumothorax.

In our present group thirteen dogs with bacteremia were treated and of these seven recovered and six died. The culture of the blood of one of the animals which recovered revealed 32 colonies, and that of another, 62 colonies per cubic centimeter. Four of the six dogs which died had an overwhelming invasion of the blood stream and in two of these autopsy revealed involvement of both lungs. Similar postmortem observations were reported by Robertson [7] for a large number of animals which were given an overwhelming infective dose.

The magnitude of the invasion of the blood stream in one of our treated animals which died (dog 523) is shown in figure 4.

The untreated control group consisted of twenty-three dogs with bacteremia, thirteen of which cannot be compared with those of the treated group, because they died within the first forty-eight hours. Of the remaining ten animals, six recovered, and four died. For those which recovered, the maximum number of colonies, respectively, ranged from 2 to 7 per cubic centimeter. No untreated dog with a culture showing more than 7 colonies survived.

TABLE 1.—*Data on Treated Dogs with Bacteremia*

Dog No.	Amount of Culture Injected, Cc.	Maximum No. of Colonies per Cc.	Comment
213	0.1	+	Recovered
725	0.1	Uncountable	Died on 4th day; both lungs involved
668	0.125	3	Recovered
671	0.125	8	Recovered
690	0.125	15	Recovered
427	0.2	8	Died on 6th day
456	0.2	Uncountable	Died on 5th day
523	0.2	Uncountable	Died on 6th day; both lungs involved
476	0.25	2	Recovered
436	0.3	Uncountable	Died on 3rd day
319	0.5	62	Recovered
1,061	0.5	10	Died on 19th day; both lungs involved
1,067	0.5	32	Recovered

TABLE 2.—*Data on Untreated Dogs with Bacteremia*

Dog No.	Amount of Culture Injected, Cc.	Maximum No. of Colonies per Cc.	Comment
617	0.1	4	Recovered
618	0.1	2	Recovered
709	0.1	9	Died on 2nd day
713	0.1	4	Died on 27th day; both lungs involved
721	0.1	6	Died on 2nd day
669	0.125	4	Recovered
670	0.125	4	Died on 22nd day (no autopsy)
754	0.125	7	Recovered
755	0.125	8	Died on 3rd day
788	0.125	+	Died on 2nd day; both lungs involved
791	0.125	Heavy growth	Died on 2nd day; both lungs involved
460	0.2	4	Died on 2nd day
461	0.2	3 (late in 5th day)	Recovered
521	0.2	20	Died on 2nd day; both lungs involved
522	0.2	7	Died on 2nd day; both lungs involved
543	0.2	6	Recovered
544	0.2	About 300	Died on 3rd day
545	0.2	Heavy growth	Died on 2nd day; both lungs involved
546	0.2	Heavy growth	Died on 2nd day
473	0.25	8	Died on 2nd day
474	0.25	16	Died on 2nd day
475	0.25	9	Died on 2nd day; both lungs involved
437	0.3	4	Died on 2nd day

In our earlier series there was not a single instance of late development of bacteremia in any animal in which treatment was instituted when the blood culture was negative. In the present series, at the time when the production of antibodies was studied a number of dogs without bacteremia were treated. One of these animals (dog 1,061) was given pneumothorax on the second day, at which time the culture of the blood was sterile. Bacteremia appeared on the next day, and then subsided and reappeared on the twelfth day. The dog died on the nineteenth day. Autopsy revealed pneumonia of both lungs. In this instance compression therapy did not prevent bacteremia.

Although in most animals with bacteremia in this series artificial pneumothorax appeared to produce a coincident diminution in the number of colonies, the blood culture for one animal (dog 456) revealed 6 colonies per cubic centimeter on the second day, and, despite treatment, overwhelming invasion of the blood stream occurred on the third day. Death took place on the fifth day. In this case pneumothorax did not control bacteremia.

SUMMARY AND CONCLUSIONS

In experimental pneumococcic lobar pneumonia in dogs, the time of appearance of specific antibodies, as determined by mouse protection, agglutination and phagocytosis tests, was uninfluenced by the use of artificial pneumothorax. The results obtained for the treated and for the untreated animals of the control group were practically identical. This corroborates the clinical findings of Blake, Howard and Hull.[1]

Experimental work is still in progress on the effect of artificial pneumothorax on lymphatic drainage in the lungs of uninfected rats. These and similar researches suggest by analogy that when artificial pneumothorax is used in the treatment of lobar pneumonia it may retard the absorption of toxins and organisms by the lymphatics.

No definite statement is permissible at this time in respect to the effect of artificial pneumothorax on pneumococcic bacteremia. With a single exception which occurred in our preceding series, compression therapy was ineffective in the presence of overwhelming invasion of the blood stream. However, it may be significant that no untreated animal recovered in which the blood culture showed more than 7 colonies per cubic centimeter, whereas in the treated group one dog with 32 and one with 62 colonies per cubic centimeter survived.

While this experimental study was in progress the following statement was made in a clinical presentation,[2] and we wish to repeat it: "Much more experimental work must be undertaken and many more patients will have to be treated early and effectively before any conclusions can be drawn in regard to the value of compression therapy in preventing invasion of the blood stream."

ABSTRACT OF DISCUSSION

DR. ALFRED STENGEL, Philadelphia: When Friedman's report and later the more convincing paper of Coghlan appeared, it was hard for some physicians to believe that pneumonia could be treated safely and effectively by this method. They and the investigators who followed established that pneumothorax properly performed may be done in cases of lobar pneumonia with safety, and that circumstance may have led to some erroneous conceptions based on the earlier papers. The results that were obtained, for example, in Coghlan's work were too good to be believed, and it seems probable that some earlier results in cases of pneumonia which had advanced beyond the stage of the first day or two probably represented spontaneous recovery of persons who were not unfavorably influenced by the pneumothorax but who would have recovered without it. Unless this

treatment is used very early in the disease, the chances of its doing definite good are not great. On the other hand, I cannot believe that pneumothorax does not do something fundamental and radical in a case of early pneumonia. The authors rejected the theory that there is speeding up of the formation of antibodies by pneumothorax, and the explanation must be sought elsewhere. I believe that for the elucidation of these points this investigation must be pursued in the future by experimentation with animals. Much may be added by the trial and error method in further clinical studies, but to obtain a real solution of the mechanism that operates here a well thought out and rather extended series of investigations of many factors that might conceivably enter into the subject will be required. This treatment is not yet on an established basis, and members of the medical profession should not assume that because certain persons occasionally have obtained brilliant results, it is an operation to be performed by those who know little more about the details than that pneumothorax has been performed and the patients have recovered. The selection of cases, the training in the production of pneumothorax and a great many other factors enter into the problem. I think that it would be unfortunate if this treatment should be accepted now as being established for pneumonia and practiced widely. Much more work must be done before it can be accepted for use as a routine.

Dr. Jesse G. M. Bullowa, New York: Since the publication of Coghlan's paper I have applied pneumothorax in the treatment of pneumonia in forty-two cases, in thirty-one before the seventy-second hour. The extent of pneumothorax was controlled by repeated roentgenograms. In my experience I have encountered little from which to infer that pneumothorax, even when applied on the first day of the illness, has beneficially influenced the progress of the disease, and some things have led me to believe that the reduction of the area of aeration may be definitely detrimental and may add the disadvantages of anoxemia to the toxemia and the possible bacteremia. I have observed an extension of the lesion in the lobe that was involved and the spread to another lobe on the side of the collapse in a patient suffering from pneumonia due to the type VIII pneumococcus treated on the third day. The lower lobe was involved and had been collapsed. The temperature decreased slightly, and on the sixth day the upper lobe of the left lung, though collapsed, became involved, and the temperature increased. The contralateral side became involved in three cases, as illustrated by a case of pneumonia due to the type V pneumococcus, in which pneumothorax was produced at the nineteenth hour for involvement of the lower lobe of the left lung. Good collapse occurred, but there was no favorable influence on the temperature and pulse from the repeated introduction of large amounts of air. The heart became displaced to the right. On the second day the blood culture became positive. Extension to the lower lobe of the right lung was found by a roentgenogram taken at the thirty-fifth hour. The patient then had to have air removed from the left side because of respiratory distress. He became delirious. On the fourth day administration of type V antiserum was begun, and he was placed in the oxygen chamber. He required 1,000,000 units. If he had been treated with serum on the first or second day, he would have required only several hundred thousand units. He recovered. In five cases the blood was invaded during treatment. There has not been dramatic relief from pain in any case. Delirium has been more frequent than usual in cases of pneumonia due to the type I pneumococcus. The problem of pneumonia is the bacteremia. If there is no bacteremia it is amazing how much a patient will stand and yet recover. With reference to the eighteen patients with pneumonia due to the type I pneumo-

coccus, six of whom died of bacteremia, I have had two hundred and thirty-nine patients with pneumonia due to the type I pneumococcus treated on the fourth and fifth days with specific serum but not with pneumothorax; thirty-three patients died, or 13.9 per cent. This treatment is not one for general practitioners or for those who have little experience with pneumonia or few facilities for treatment. Of one hundred cases of seven types of pneumococcic pneumonia, in which no specific treatment was given, in some the disease terminated on the first or second day. In many cases pneumonia due to the type I pneumococcus terminated on the fifth, sixth or seventh day. In most cases the condition terminated between the fourth and the twelfth day. The curve for each type was somewhat different from that of the others. Until the appearance of such a chart is changed by the use of a treatment for pneumonia, that treatment cannot be said to be beneficial.

Dr. Francis G. Blake, New Haven, Conn.: My associates and I have made a considerable number of studies on the mechanism involved. We have found no evidence of accelerated production of antibodies or evidence in support of the view advanced by Holmes and Randolph that the production of pneumothorax induces crisis by expelling exudate from occluded bronchi. We have been able to demonstrate by fluoroscopic study in a considerable number of cases that there is complete immobilization of the inflamed lung so far as respiratory movement is concerned. It is our opinion that this is probably the mechanism by which artificial pneumothorax exerts its effects. The eighteen cases of pneumonia due to the type I pneumococcus in our series, in six of which the outcome was fatal, were those of a late stage or of adhesions, and type I serum also was given in three cases. In our experience, as already stated, the treatment of pneumonia after the third day with artificial pneumothorax accomplished nothing in the way of cure. I agree with Dr. Stengel that it is too soon to use the method widely, because all the conditions under which it is or is not beneficial are not yet known.

RELATIONSHIP OF FELTY'S AND ALLIED SYNDROMES TO SEPSIS LENTA

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In 1924, Felty [1] described the occurrence in five middle-aged adults of a syndrome characterized by chronic deforming arthritis, splenomegaly, lymphadenopathy, leukopenia and cutaneous pigmentation. Secondary anemia was present in all but one case, and in two patients low grade fever was detected. Felty apparently assumed that the clinical picture he had described had hitherto been unobserved in adults and offered two explanations for this unusual syndrome, namely, that the manifestations are part of one pathologic process, the counterpart in the adult of Still's disease of childhood, and that the syndrome is merely the confusion of two separate clinical entities, i. e., chronic arthritis and Banti's disease, occurring coincidentally in the same person. Felty favored the former explanation chiefly on the basis of the law of probability and concluded that he was dealing with a distinct clinical entity caused by a "noxa which simultaneously affects the joints, spleen and blood leukocytes and in 3 of 5 cases the lymph nodes." No reference to Felty's article appeared in American literature for eight years, at the end of which time Hanrahan and Miller [2] recorded the case of a woman of 50, in whom chronic arthritis, splenomegaly, anemia, leukopenia and marked loss of weight were noted. Nodules, which were dusky red and painful, also were observed. A blood culture proved sterile. Hanrahan and Miller, who considered their case an example of Felty's syndrome, felt "that the marked splenomegaly and leucopenia were in themselves sufficient indication to warrant the operation (splenectomy) regardless of a possible favorable effect on the arthritis." Following the removal of the spleen the patient felt better generally and the arthritis improved greatly. The number of white cells increased from a count which varied between 640 and 1,600 before operation to 12,000 after operation. Culture of the splenic tissue proved sterile. Micro-

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1. Felty, A. R.: Chronic Arthritis in the Adult, Associated with Splenomegaly and Leukopenia: A Report of Five Cases of an Unusual Clinical Syndrome, Bull. Johns Hopkins Hosp. **35**:16 (Jan.) 1924.

2. Hanrahan, E. M., Jr., and Miller, S. R.: Effect of Splenectomy in Felty's Syndrome, J. A. M. A. **99**:1247 (Oct. 8) 1932.

scopically, swelling of the lining endothelial cells, erythrophagocytosis and infiltration of the pulp by plasma cells were noted. The question of the nature of the underlying disease process was left sub judice.

During the latter part of 1933 and the early part of 1934 three American publications dealing with Felty's syndrome appeared in medical literature. The first article, by one of us (H. A. S.),[3] was merely a summary of a brief paper given before the Central Society for Clinical Research on Oct. 28, 1933. The second article, which was written by Craven [4] and which appeared in March 1934, contained an account of a man who presented all five cardinal features of Felty's syndrome and in addition a subfebrile temperature. Splenectomy afforded only transient benefit. Sections of the spleen exhibited changes similar to those described by Hanrahan and Miller. Culture of an excised superficial lymph node yielded a green-producing streptococcus. Craven did not discuss the subject of etiology of Felty's syndrome and made no comment regarding the possible significance of the positive bacteriologic observation. More recently (April 1934) Price and Schoenfeld [5] described the case of a man 59 years old, who suffered from recurrent arthritis, splenomegaly and leukopenia. The arthritis was not apparently of the deforming type, and pigmentation and lymphadenopathy were lacking. Signs of fibrinous pleurisy were followed two weeks later by a pericardial friction rub, which disappeared after several days. The rub recurred ten days later, and on the night of its reappearance, just preceding the day on which splenectomy was to be performed, the patient died. The microscopic changes in the spleen consisted of "diffuse fibrosis with dilatation of the splenic sinuses. The latter showed areas of myeloid activity, with numerous plasma cells and eosinophils and an occasional bone marrow giant cell. There was diffuse, chronic septic splenitis." Price and Schoenfeld concluded that the case clinically was one of Felty's syndrome. They were led to believe that the splenomegaly of Felty's syndrome belonged to the same group of splenic diseases described by Giffin [6] and by Ward [7] owing to a variety of etiologic (infectious) factors.

Until the appearance of the brief communication by one of us (H. A. S.),[3] which appeared in December 1933, the association of deforming

3. Singer, H. A.: The Etiology of Felty's and Related Syndromes, J. A. M. A. **101**:2078 (Dec. 23) 1933.

4. Craven, E. B., Jr.: Splenectomy in Chronic Arthritis, Associated with Splenomegaly and Leukopenia (Felty's Syndrome), J. A. M. A. **102**:823 (March 17) 1934.

5. Price, A. E., and Schoenfeld, J. B.: Felty's Syndrome: Report of Case with Complete Post-Mortem Findings, Ann. Int. Med. **7**:1230 (April) 1934.

6. Giffin, quoted by Price and Schoenfeld.[5]

7. Ward, quoted by Price and Schoenfeld.[5]

arthritis, splenomegaly and lymphadenopathy in adults was considered, so far as recent American literature is concerned, unique. Thus Felty looked on the syndrome he described as a new entity, the counterpart of Still's disease in the adult. Hanrahan and Miller [2] apparently considered Felty to be the first to call attention to the syndrome to which they prefixed Felty's name. In the article by Craven [4] published in March 1934, reference is made to the treatises of Felty and Hanrahan and Miller, followed by the statement, "In the voluminous literature dealing with chronic arthritis, splenomegaly and leukopenia as separate entities, the simultaneous occurrence of the three abnormalities is not mentioned except in these two papers." Price and Schoenfeld,[5] whose article appeared in April 1934, attempted to show that the association of arthritis, splenomegaly and leukopenia is not as rare as it is considered by other American writers, but they failed to take cognizance of or to refer to the extensive foreign and older domestic literature which is to be summarized here.

Before a medical group, Still [8] in 1896 described a specific form of chronic joint disease in children since known by his name. The twelve distinctive cases which he separated from a group of twenty-two instances of chronic arthritis in children were characterized by "chronic, progressive enlargement of joints, associated with general enlargement of glands and spleen." A tendency to moderate anemia and arrest of physical development were noted, and in four cases there was undue prominence of the eyes. The most striking features in this form of juvenile chronic arthritis, viz., the involvement of the lymphatic glands and the enlargement of the spleen, were not found, as far as Still knew, in the adult. In three cases autopsy was performed, and in addition to the presence of a firm, enlarged spleen an adherent pericardium was found in all three. Still mentioned that the etiology was uncertain. Earlier in the year in which Still described the disease in children now known by his name, Chauffard and Ramond [9] reported the association of *adénopathies sus-articulaires* with chronic infectious arthritis in seven adults. Enlargement of the spleen was absent or at least not mentioned. The arthritis, which was quite different from the senile type, was characterized by paroxysmal febrile periods alternating with periods of remission, and the adenopathy was noted especially in the region of the affected joints. In two cases evidence of cardiac lesions existed. None of the cases were followed to autopsy. Chauffard and Ramond concluded that the adenopathy was secondary to the arthropathy, both lesions developing from the same infectious source. After a

8. Still, G. F.: On a Form of Chronic Joint Disease in Children, Med.-Chir. Tr., London **80**:47, 1896-1897.

9. Chauffard, A., and Ramond, F.: Des adénopathies dans le rhumatisme chronique infectieux, Rev. de méd., Paris **16**:345 (May) 1896.

great deal of bacteriologic work with lymph glands and articular fluid a diplococcus was finally isolated from material taken from one patient.

Since the time of Still [8] and of Chauffard and Ramond,[9] a rather voluminous literature has appeared dealing with the presence in both children and adults of chronic arthritis associated with either adenopathy or splenomegaly or both and variably with leukopenia, pigmentation, secondary anemia and subcutaneous nodules. Bannatyne and Wohlman [10] in 1896 pointed out that rheumatoid arthritis commences as a progressive arthritis, deforming in nature, and later anemia, enlarged glands (especially in children) and such trophic disorders of the skin as pigmentation occur. Delcourt [11] in 1898 described a case of chronic arthritis of the Still type in a 4 year old child, with autopsy. In 1904, McCrae,[12] in reporting one hundred and ten cases of arthritis deformans from the service of Professor Osler at Johns Hopkins University, noted a general adenopathy in thirteen, enlargement of the spleen in four, marked pigmentation in eight and a leukocyte count of 5,000 or less in six cases. Two examples of Still's malady were included. Weber [13] described two cases of Still's disease in 1905 and referred also to the malady of a 16 year old girl with a rheumatoid condition and a palpable spleen as "probably a variety of Still's type occurring in an older patient." Von Jaksch [14] early in the twentieth century reported the occurrence in a 45 year old patient of chronic arthritis, a huge spleen, anemia and leukopenia, all of which he explained on the basis of a "gouty diathesis." A report of the autopsy was included. Additional reports on Still's disease proper multiplied by such leaps and bounds that by 1914 Ibrahim [15] had succeeded in collecting from the world literature two hundred and seventy-three cases, to which he added six of his own.

The first mention of the term Still-Chauffard's disease, used by European authors as corresponding to Felty's syndrome, was made by Pollitzer,[16] who in 1914 described two adult patients with chronic

10. Bannatyne, G. A., and Wohlman, A. S.: Rheumatoid Arthritis: Its Clinical History, Etiology and Treatment, Lancet **1**:1120 (April 25) 1896.

11. Delcourt, A.: Rhumatisme articulaire noueux chez les enfants, Rev. mens. d. mal. de l'enf. **16**:329, 1898.

12. McCrae, T.: Arthritis Deformans: The Report of One Hundred and Ten Cases from the Johns Hopkins Hospital, J. A. M. A. **42**:1 (Jan. 2) 1904.

13. Weber, F. P.: Still's Type of Chronic Joint Disease in Children and the So-Called "Tuberculous Rheumatism," Brit. J. Child. Dis. **2**:208, 1905.

14. von Jaksch, A.: Arthritis urica, Megalosplenie und Leukopenie, Deutsche med. Wchnschr. **34**:634, 1908.

15. Ibrahim, J.: Die chronische Arthritis im Kindesalter, Ztschr. f. orthop. Chir. **34**:213, 1914.

16. Pollitzer, H.: Ueber chronischen Gelenkrheumatismus mit Drüsenschwellung und Milztumor (Typus Still-Chauffard), Med. Klin. **10**:1511 (Sept. 27) 1914.

arthritis, enlarged lymph nodes and splenic tumor of "typus Still-Chauffard." In subsequent reports by continental writers dealing with the Still syndrome, the adult form (Still-Chauffard's disease) was sharply separated from the juvenile type. The number of cases recorded in adults indicates that the disease is not nearly as rare or as new as suggested in American literature. Schmidt [17] in 1917 recorded a case of *Still-Chauffardscher Erkrankung* occurring in a 40 year old white man afflicted with chronic generalized arthritis, universal adenopathy and enlargement of the spleen. Bacteriologic studies of blood, fluid from the joints and excised nodes, both smears and cultures, gave uniformly negative results. Goldstein [18] described a woman 38 years old with a typical Still-Chauffard syndrome, including marked leukopenia, with a white cell count of from 900 to 1,600, but lacking pigmentation. A culture of the blood gave negative results. In Herman's [19] case a 27 year old patient had deforming arthritis and enlarged nodes and spleen. Vinkuroff and Levi [20] reported two cases, and because of negative bacteriologic observations they concluded that the exciting agent of this form of chronic arthritis is as yet undiscovered. Steinitz and Casperfürstenheim [21] related the case of a 31 year old patient with a Still-Chauffard syndrome, including autopsy. Chevallier [22] gave a complete and comprehensive discussion of various aspects of the Still-Chauffard and related syndromes and was the first to suggest removal of the spleen with the idea of inducing retrogression of the arthropathy. Chevallier and Heuyer [23] reported a case illustrating a mild variety of Still-Chauffard's disease. Weissenbach and others [24] reported several

17. Schmidt, R.: Ein Fall von Still-Chauffardscher Erkrankung, Med. Klin. **13**:1076 (Oct. 7) 1917.

18. Goldstein, W.: Stillsches Krankheitsbild beim Erwachsenen, Med. Klin. **22**:1527 (Oct. 1) 1926.

19. Herman, K.: Ueber Still-Disease, Klin. Wchnschr. **6**:1807 (Sept. 17) 1927.

20. Vinkuroff, I. Y., and Levi, G. S.: Rare Clinical Cases of Chronic Diseases of Joints (Still-Chauffard Disease), Odesskii med. zhur. **3**:575 (Oct. 28) 1928.

21. Steinitz, H., and Casperfürstenheim, A.: Abortivform von Stillscher Krankheit mit Sclerodermie, Med. Klin. **26**:700 (May 9) 1930.

22. Chevallier, P.: La maladie de Chauffard-Still et les syndromes voisins, Rev. de méd., Paris **47**:77 (Feb.) 1930.

23. Chevallier, P., and Heuyer, G.: Syndrome rhumatismal et adénopathique atteignant les membres inférieurs et évoluant par poussées qui guérrissent (forme inférieure et attenuée de la maladie de Chauffard-Still), Bull. et mém. Soc. méd. d. hôp. de Paris **54**:65 (Jan.) 1930.

24. Weissenbach, R. J.; Françon, F.; Gerbay, F., and Robert, P.: Deux cas de syndrome de Chauffard-Still, Bull. et mém. Soc. méd. d. hôp. de Paris **55**:172 (Jan.) 1931.

cases, and in a later article Weissenbach and Françon [25] presented an excellent general résumé of the subject. A 40 year old patient with Still-Chauffard's disease was described by Lemierre and Mahoudeau-Campoyer,[26] who employed and recommended the intravenous injection of sodium salicylate. Etienne and others,[27] Saad,[28] Frugoni,[29] Costa [30] and Fieschi,[31] each reported one case, the last author recording pathologic observations. Giordano [32] presented ten case reports with a thorough review of the subject. Articles by Kramsztyk,[33] Micheli [34] and Ocaranza [35] probably included case reports but were not available to us. Rather recently (1933) Moltke [36] attempted to establish the similarity between Still's disease and the condition observed in his four cases of subchronic or chronic polyarthritis in young men with subfebrile temperature, polyadenitis and a disturbance of the general condition. Graber-Duvernay [37] described recently what he termed the Still-Chauffard syndrome occurring in six adults in all of whom adenopathy of the satellite type occurred but in only two of whom splenomegaly was present.

Of prime importance in connection with the subject of Still's disease and related syndromes is the etiology. Is there merely one cause or are

25. Weissenbach, R. J., and Françon, F.: Le syndrome de Chauffard-Still. Rhumatisme chronique fibreux déformant progressif avec adénopathies et splénomégalie. Sa place en nosologie, Presse méd. **39**:1197 (Aug. 12) 1931.

26. Lemierre, A., and Mahoudeau-Campoyer, D.: Efficacité des injections intraveineuses de salicylate de soude dans un cas de maladie de Chauffard-Still, Gaz. d. hôp. **105**:1029 (July 9) 1932.

27. Etienne, G.; Drouet, P. L.; Touyot, P., and Richon, J.: Un cas de maladie Chauffard-Still, Bull. et mém. Soc. méd. d. hôp. de Paris **56**:1398 (Nov. 4) 1932.

28. Saad, B.: Un cas de maladie de Chauffard-Still, Bull. Soc. franç. de dermat. et syph. **39**:757 (June) 1932.

29. Frugoni, C.: Morbo di Still-Chauffard, Policlinico (sez. prat.) **39**:1077 (July 11) 1932.

30. Costa, A.: Un caso di sindrome di Still, Arch. per le sc. med. **56**:161 (March) 1932.

31. Fieschi, A.: Poliartropatia subacuta tipo Still-Chauffard, Riforma med. **48**:511 (April 2) 1932.

32. Giordano, C.: Contributo allo studio del morbo di Still-Chauffard, Arch. per le sc. med. **55**:319 (July) 1931.

33. Kramsztyk, J.: Gelenkrheumatismus mit Lymphdrüsenschwellung (Still-Chauffard), Pedjatrja polska **2**:2, 1922.

34. Micheli, F.: Sur la maladie de Still-Chauffard, Acta rheumatol. **3**:11 (Feb.) 1931.

35. Ocaranza, F.: A propósito de un caso de enfermedad frustrada de Chauffard-Still, Medicina, México **12**:417 (Aug. 25) 1932.

36. Moltke, O.: Still's Disease in Adults, Ugesk. f. læger **95**:737 (June 29) 1933.

37. Graber-Duvernay, J.: Six observations de syndrome de Chauffard-Still chez l'adulte, Acta med. Scandinav. **81**:63, 1934.

there several different causes of the symptom complex under discussion? The micro-organisms which have been suspected include those of tuberculosis, syphilis and chronic low grade sepsis. These infections will be dealt with later. Other factors which have an etiologic bearing have been suggested. For instance, a possible endocrine element has been emphasized by some authors because of the associated exophthalmos, slight in the cases of Still,[8] Pollitzer [16] and Graber-Duvernay [37] and more marked in those of Koeppe,[38] Reimold and Stoeber [39] and Weissenbach and his associates.[24] In the last instance an actual hyperthyroidism, with a basal metabolic rate of plus 44 per cent was found. Vinkuroff and Levi [20] mentioned the thyrogenic arthritis of Veljaminov as a possibility but not a probability. The association of scleroderma was noted by Stöltzner,[40] Strauss,[41] Stoye [42] and Steinitz and Casperfürstenheim.[21] Pollitzer [16] and later Bauer,[43] Schmidt,[17] Muncke [44] and Goldstein [18] attributed at least part of the peculiarities of these syndromes to the existence of a lymphatic constitution or predisposition. However, they, as well as most other investigators, stated the belief that an infection is the primary etiologic agent and that the lymphatic constitution accounts merely for the peculiar response on the part of the spleen and lymph nodes.

A tuberculous rheumatism, such as Poncet [45] described in 1901, in three frankly tuberculous patients with arthritic manifestations has been assumed by later authors to be present in Still's disease. The evidence for a Koch infection is not at all convincing, as a review of the reports pertaining to this phase of the subject will disclose. Edsall [46] cited a case of Still's disease on a tuberculous basis in a 13 year old boy in whom the injection of old tuberculin produced a definite rise in temperature and pains in the joints. Although no evidence of tuberculosis

38. Koeppe, H.: Ein Fall von "Still'scher Krankheit," Jahrb. f. Kinderh. **76**:707, 1912.

39. Reimold, W., and Stoeber, T.: Beiträge zum Problem der Stillschen Krankheit, Monatschr. f. Kinderh. **31**:597 (March) 1926.

40. Stöltzner: Stillsche Krankheit mit Sklerodermie, Deutsche med. Wchnschr. **50**:1136, 1924.

41. Strauss, H.: Ueber Stillsche Krankheit, Med. Klin. **22**:1247 (Aug. 13) 1926.

42. Stoye, W.: Ein Beitrag zur Ätiologie der Stillschen-Krankheit und der herdförmigen Sklerodermie, Ztschr. f. Kinderh. **41**:538, 1926.

43. Bauer, J.: Die konstitutionelle Disposition zu inneren Krankheiten, Berlin, Julius Springer, 1917.

44. Muncke, A.: Ein Beitrag zur Pathologie der Stillschen Krankheit, Med. Klin. **20**:1502 (Oct. 26) 1924.

45. Poncet, A.: Rhumatisme tuberculeux ou pseudo-rhumatisme d'origine bacillaire, Gaz. d. hôp. **74**:817 (July 25) 1901.

46. Edsall, D. L.: Concerning the Nature of Still's Type of Chronic Polyarthritis in Childhood, Arch. Pediat. **21**:175, 1904.

was obtained in a lymph node removed from the axilla, in an emulsion of several nodes a large number of acid-fast organisms considered to be typical Koch bacilli were found. However, the injection of this same emulsion into guinea-pigs resulted in no change in the health of the animals, and after five weeks no evidence of tuberculosis was detected in the internal organs. The only evidence that Weber [13] had for diagnosing the condition in his second case as tuberculous rheumatism was the production of a general reaction, including a temperature of 101 F., by the injection of old tuberculin used for the Pirquet test. No local reaction occurred. One of Piske's [47] patients, an 8 year old girl with polyarthritis, enlarged nodes and spleen, definite involvement of the lungs and a negative Pirquet reaction and culture of the blood, was found at autopsy to have miliary tubercles in various organs, including the spleen. However, the superficial nodes were not involved. Piske concluded that he was dealing with Poncet's type of tuberculous rheumatism. Cozzolino [48] in 1914 assumed tuberculosis to be the cause of an arthritis and adenitis in a 7 year old patient on the basis solely of a positive reaction to tuberculin. For the etiologic agent of two cases of Still's malady, Longo [49] mentioned tuberculosis as a good possibility but included no evidence in favor of it, for in both instances the reaction to tuberculin was negative and neither patient came to autopsy. With regard to syphilis, there is even less evidence for the assumption that it causes Still's disease or related syndromes. The only case in which an etiology of syphilis might be entertained is that reported by Weissenbach and Françon.[25] These authors reported the case of a 15 year old girl with hereditary syphilis in whom a Still-Chauffard syndrome and certain thyro-ovarian disturbances retrogressed under antisyphilitic and endocrine treatment.

Since Chauffard and Ramond [9] in 1896 searched diligently but unsuccessfully for the causative organism, a great deal of bacteriologic work has been performed in an attempt to find the specific etiologic factor. Piske [47] made cultures of blood in a search for streptococci or staphylococci but failed to recover any. Pisek,[50] an American author, stated: "The polyarthritis described by Still seems to be the result of a chronic sepsis, which while not sufficiently potent to completely overpower the young organism, has destroyed resistance by enfeebling the

47. Piske, J.: Zur Kenntnis der Stillschen Krankheit, Med. Klin. **9**:1968 (Nov. 30) 1913.

48. Cozzolino, O.: Un caso di reumatismo articolare cronico tubercoloso in bambina (con la sintomatologia del morbo di Still), Pediatria **21**:401, 1913.

49. Longo, A.: Contributo allo studio della cosi detta malattia di Still, Riv. di clin. pediat. **15**:225, 1917.

50. Pisek, G. R.: The Present Status of Still's Disease, Arch. Diagnosis **2**:355, 1909.

phagocytic power of the blood and lowering the activity of the lymphatics." His cultures of material aspirated from the joints, however, remained sterile. Westmeyer [51] suspected chronic sepsis because of recurrent chills and fever, but two cultures of the blood gave negative results. Litchfield [52] in 1922 stated: "Despite the absence of demonstrable bacterial causation (negative blood culture), the assumption of a continual or recurrent bacteremia of low-grade with joint deposition seems plausible." Iseke,[53] by making cultures of material removed post mortem from the spleen, lungs, endocardium and middle ear of a 2 year old child with Still's syndrome, was able to obtain Streptococcus viridans in almost pure form. He concluded that a chronic sepsis possibly of an endocarditis lenta type was the cause of Still's disease. The next year Johannson,[54] in reporting a case, concluded that Still's disease is the expression of a chronic sepsis. Strauss [41] in 1926, in spite of negative results from cultures of blood removed post mortem and negative bacteriologic results from cultures of tissue, joints and nodes, considered the disease a "lenteszierender" streptococcic sepsis, in which there is a peculiar type of mesenchymal reaction on the part of the spleen, lymph nodes, pericardium and pleura.

The first investigators to recover the probable etiologic agent from the blood stream during life were Reimold and Stoeber.[39] After repeated failures they finally succeeded in culturing from the circulating blood of a child with Still's disease a pure growth of Str. viridans. Stoye [42] found nonhemolytic (indifferent) streptococci in the blood of the heart of a patient with Still's disease, who, however, died of bronchopneumonia. Debré and others [55] described a boy of 10 years with a typical Still complex associated with endocarditis of the lenta type. Although cultures of the blood gave negative results, the authors concluded that the entire picture was the result of sepsis due to Str. viridans. In support of their contention they referred to an observation of an absolutely characteristic endocarditis lenta, verified by the finding of Str. viridans in the circulating blood, occurring in an adult with chronic deforming arthritis. Recently Bennholdt-Thomsen [56] recorded the recovery of

51. Westmeyer, J.: Der chronische Gelenkrheumatismus im Kindesalter, Jahrb. f. Kinderh. **81**:69, 1915.

52. Litchfield, H. R.: Still's Disease (Atrophic Arthritis), Arch. Pediat. **39**:107, 1922.

53. Iseke, G.: Zur Aetiologie der Stillschen Krankheit, Ztschr. f. Kinderh. **35**:315 (June) 1923.

54. Johannson, N.: Ein Beitrag zur Kenntnis der "Still'schen Krankheit," Acta pædiat. **2**:354, 1924.

55. Debré, R.; Broca, R., and Lamy, M.: Forme endocardique de la maladie de Still, Arch. de méd. d. enf. **33**:212 (April) 1930.

56. Bennholdt-Thomsen, C.: Zur Stillschen Krankheit, Klin. Wchnschr. **13**: 236 (Feb. 10) 1934.

Staphylococcus aureus four times and of Str. viridans once from the blood of a 2½ year old child with Still's disease. He viewed the syndrome as a slowly developing form of sepsis of the lenta type, the infectious agent being Str. viridans. As to whether Staph. aureus plays an accompanying rôle must be determined, he thought, by further investigation. The data in connection with two adult patients we have studied lend support to the view that Felty's syndrome is the result of a low grade sepsis, probably streptococcic. The evidence pointing to a chronic sepsis of the lenta type is not limited to the bacteriologic results but includes also the anatomic observations. Case 1, although observed later than case 2, is presented first since the former offers a more typical picture of the condition from the standpoint of both clinical examination and necropsy.

REPORT OF CASES

Case 1.—I. W., a white man 55 years of age, dated the onset of his malady back to 1924, when he acquired polyarthritis, affecting the joints of the hands, shoulders, knees and ankles. The involved joints were red, swollen, tender and painful. At the end of three months' confinement to bed, although not completely recovered, the patient was able to be up and about. Within the next four years, coinciding with exacerbations of arthritis, subcutaneous nodules appeared, varying in size from that of a pea to that of a walnut, which were situated near the affected joints. At first these nodules were tender, but later they became painless. During the period in which the subcutaneous nodules were prominent the patient attended a large clinic, where the diagnosis of secondary anemia and chronic infectious arthritis was made, although gout could not be ruled out. The patient's tonsils were removed, the teeth extracted and a chronic prostatic inflammation treated by various measures. Physical therapy was advised. The subsequent course of the arthritis was marked by remissions and exacerbations. In the meantime deformity of the hands developed. In 1931, the patient entered another hospital for observation. At this time, enlargement of the spleen and pigmented areas on the legs were noted in addition to the deforming arthritis. The examination of the blood revealed an erythrocyte count of 3,200,000, a hemoglobin content of 65 per cent and a leukocyte count varying from 2,400 to 8,700, with an average of 5,100 for seven determinations. The differential count showed a marked preponderance of lymphocytes, varying from 58 to 80 per cent. A biopsy of an inguinal lymph gland was reported as showing the histologic picture of chronic lymphadenitis. The condition was diagnosed on discharge as aleukemic leukemia, with complicating chronic atrophic arthritis. Because of his disabling arthritis the patient was sent to the Oak Forest Infirmary, the home for incurable patients of Cook County. The patient left Oak Forest to enter the Cook County Hospital on Nov. 9, 1932.

On entrance the patient was moderately undernourished and not acutely ill. The temperature and the pulse and respiratory rates were normal. The heart was not enlarged, and no abnormal sounds were heard. The blood pressure was 130 systolic and 70 diastolic. The liver, which was palpable 6 cm. below the costal border, was not tender. The spleen was firm, smooth and greatly enlarged, reaching below the umbilicus and projecting above the level of the remainder of the abdomen (figs. 1 and 2). Enlarged lymph nodes were noted in the cervical, axillary, epitrochlear and inguinal regions. Deforming arthritic changes were

present in the joints of both hands, the fingers being fixed in flexion at the metacarpophalangeal joints. Located at the left elbow, right knee and right inguinal regions were old surgical scars, the sites from which specimens were taken for biopsy. The skin had a generalized light tan muddy discoloration, with numerous well demarcated patches of dark brown pigmentation of variable size located on the lower extremities. There was bilateral hallux valgus. Examination of the blood yielded an erythrocyte count of 3,450,000, a hemoglobin content of 63 per cent, a leukocyte count which varied from 950 to 1,500, and a differential count

Fig. 1 (case 1).—Photograph of an adult with Felty's syndrome, illustrating arthritis deformans of the hands, splenomegaly (indicated by prominence of the abdomen; fig. 2) and patchy pigmentation of the lower extremities. The lymphadenopathy is not sufficiently marked to be discerned. The white blood count ranged from 950 to 1,500 per cubic millimeter.

of 24 per cent polymorphonuclears, 72 per cent lymphocytes and 4 per cent monocytes. A splenic puncture revealed the presence of the following cells in the aspirated material; polymorphonuclear leukocytes 2 per cent, eosinophils 1 per cent, lymphocytes 95 per cent and monocytes 2 per cent. The lymphocytes, which measured up to 16 microns in diameter, had coarsely trabeculated nuclei

and homogeneous basophilic cytoplasm. Many basket cells, numerous polychromatophilic erythrocytes and an occasional normoblast were seen. Chemical studies of the blood afforded no noteworthy information. The Wassermann reaction of the blood was negative. A roentgenogram of the affected joints showed marked deformity but no bony changes. Roentgenograms of the lungs disclosed an area of calcification in the apex of the upper lobe of the left lung.

The presence of deforming arthritis, in association with splenomegaly, lymphadenopathy, leukopenia, secondary anemia and the peculiar form of pigmentation of the legs, led to the diagnosis of a Still-Chauffard or Felty syndrome. The investigation to determine if possible the underlying cause furnished evidence pointing to the existence of a sepsis lenta. For instance, a biopsy of an inguinal lymph node showed changes indicative of a chronic low grade infectious process, and a blood culture yielded a pure growth of Str. viridans. On the basis of the recent experience of Hanrahan and Miller, the advisability of splenectomy was considered and was mentioned to the patient. Since skepticism with regard to the ultimate benefit was expressed, the patient declined to take the risk. Treatment was practically entirely symptomatic. The subsequent course was char-

Fig. 2 (case 1).—With the patient supine the enlarged spleen is seen to project above the level of the remainder of the abdomen.

acterized by short periods of fever, a temperature generally subfebrile but occasionally reaching from 101 to 102 F., an increasing anemia, progressive weakness and repeated showers of petechial hemorrhages. The clinical resemblance to subacute bacterial endocarditis was very striking at this time. About six weeks before the patient's death, evidences of cardiac decompensation supervened. The patient became progressively weaker and died on April 25, 1933, six and one-half months after entrance to the hospital.

Autopsy.—The macroscopic and histologic examinations were made by Dr. R. H. Jaffé. The most informative changes were disclosed by microscopic examination.

Macroscopic Examination: The salient changes observed post mortem can be briefly summarized as follows: Externally there was evidence of marked loss of weight and of anemia. In the skin of the upper eyelids were many purple-red petechiae, measuring up to 2 mm. in diameter. Numerous similar hemorrhagic spots were seen in the skin of the lower extremities, where, in addition, irregular, discrete and confluent dark gray-brown areas with geographic outlines measuring as much as 5 cm. in one dimension were found. The fingers were fixed in flexion with slight nodular deformities at the metacarpophalangeal articulations. The superficial lymph glands were enlarged, firm and discrete and measured up to 1.5 cm. in diameter. There was an extreme hallux valgus involving both feet.

In the abdominal cavity was about 3,000 cc. of a brownish cloudy fluid. In the omentum and mesentery were numerous recent petechial hemorrhages. The lower pole of the spleen extended 6 cm. below the costal arch. The lower border of the liver was 13 cm. below the xiphoid process and 7 cm. below the costal arch. Both pleural cavities were obliterated by firm fibrous adhesions. The pericardial sac was obliterated by loose fibrous adhesions. The heart weighed 340 Gm. The left and right ventricular walls measured 15 and 3 mm., respectively. The myocardium was dark, brown-gray and friable. The valves of the heart were unchanged. The aorta and some of its main branches contained hyaline and fatty plaques. The left coronary artery presented similar changes and in addition calcified plaques. The lungs were subcrepitant and moist in portions. In the subapical region of the left lung was an indurated, deeply pigmented fibrosed area in which were several fibrocalcareous nodules, measuring up to 2 mm. in diameter.

The spleen weighed 1,710 Gm. and measured 10 by 18 by 30 cm. It was of firm consistency, and attached to its thickened capsule were numerous fibrous adhesions. Its sectioned surface was deep purple-red, mottled with lighter areas. The trabeculae and follicles were distinct, the latter light gray and the size of a pinhead. The liver, which weighed 1,930 Gm., was firm, smooth and purple-brown, with the capsule thickened in places. The sectioned surface was brown-gray with purple-red acinar markings. The kidneys together weighed 310 Gm. Each kidney was moderately firm; the capsule stripped with ease, leaving a smooth surface which was purple-gray with many purple patches up to the size of a pinhead. The sectioned surface showed the cortex to be 4 mm. thick, light purple-gray and studded with purple-red areas from the size of a pinhead to that of a pinpoint. The bone marrow was soft and a pale rust-brown.

Microscopic Examination: Only those organs and structures in which significant changes were found are described.

In the spleen the endothelial cells lining the sinusoids were quite prominent, being swollen and increased in number. They exhibited a more marked cytoplasmatic body and took an increased basophilic stain (fig. 3). The sinusoids and cords were packed with red blood cells. Among the red cells in the sinusoids were desquamated endothelial cells. In the pulp were numerous plasma cells, often showing signs of degeneration (pyknosis of the nucleus), a moderate number of small and medium sized lymphocytes and a considerable number of free histiocytes with kidney-shaped nuclei and engulfed blood pigment. Single normoblasts and neutrophilic leukocytes with indistinct granulation and a few oxyphilic leukocytes were also found. The follicles were of medium size and lymphocytic, and the reticulum near the center often was hyalinized. In the trabeculae were elongated, flat, iron-containing cells.

The structure of the liver was somewhat irregular because of circumscribed areas of alteration of liver cells. Streaks of shrunken liver cells with pyknotic nuclei permeated the lobules and extended in different directions, often from the central vein toward the periportal tissue. In these areas capillaries were congested. Other areas of atrophy of the liver cells, which were more focal and marked by a proliferation of the Kupffer cells, were seen. Excluding these two types of circumscribed parenchymatous alteration, the liver cells were well preserved and occasionally contained large droplets of fat. Brownish pigment granules were found in many of the liver cells, especially near the central veins and in the areas of atrophy. Throughout the lobules the Kupffer cells were greatly swollen, with ample cytoplasm, and exhibited at times nuclei which were the shape of a

kidney bean (fig. 4). In the sinusoids were single plasma cells and many free rounded histiocytic elements containing blood pigment. The periportal tissue was infiltrated by lymphocytes and plasma cells.

The sinuses of the abdominal lymph nodes (peripancreatic, peribiliary) were wide and lined by swollen endothelium and contained erythrocytes and proliferated endothelial cells, many of which contained red blood cells or blood pigment. The secondary follicles were small, with histiocytic centers. Groups of reticular cells filled with iron pigment were seen.

Skin taken from the thigh showed a great deal of iron pigment in the cutis, enclosed in elongated, often spindle-shaped, cells. Accumulations of these iron-containing cells were particularly evident about the sweat glands in the form of

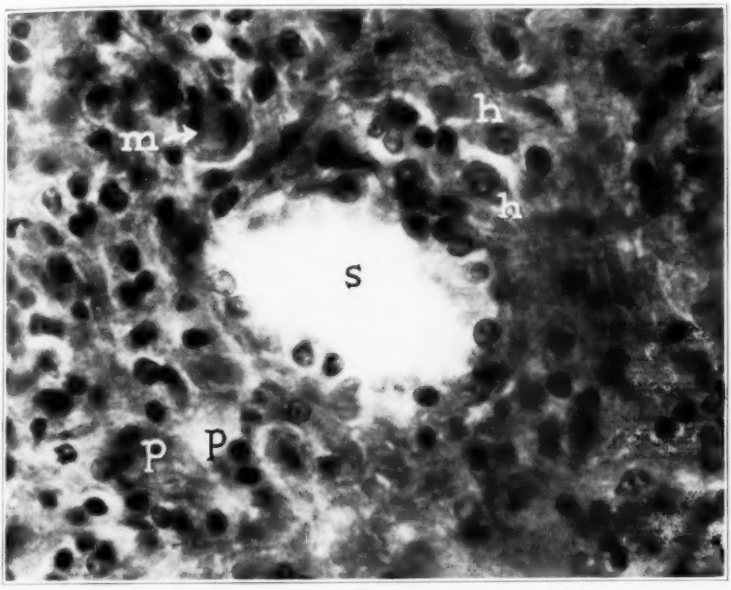

Fig. 3 (case 1).—Photomicrograph of a frozen section of spleen stained with hematoxylin and eosin. The lining of the splenic sinus (*s*) is unusually prominent, owing to swelling and increase in number of the endothelial cells. Bordering the sinus is a large macrophage (*m*) with engulfed erythrocytes. Other histiocytic cells (*h*) and plasma cells (*p*) are distributed throughout the pulp. Magnification, × 600.

heavy coats. The adventitial cells of the cutaneous capillaries were engorged with iron granules also. The melanin in the basal layer of the epidermis was not increased.

Throughout the bone marrow there was marked congestion, and the fatty portions exhibited signs of atrophy and formation of a net of fibrin. The reticulum was inconspicuous. The endothelium of the blood vessels was somewhat prominent.

The cellularity of the bone marrow was 37 per cent (the fat tissue representing the remaining 63 per cent). The neutrophilic myelocytes showed signs of severe alteration, intact granulation being completely absent. In place of the normal granules there were found small, purple-pink, pale vacuoles having a tendency to fuse. The nuclei of the myelocytes were round or bean-shaped, and the chromatin was broken up in coarse, round or angular granules which were linked by ill defined threads. The nucleoli were difficult to differentiate from the chromatin granules. However, the nuclear membranes were usually intact. Some of the nuclei were shrunken and pyknotic. An abortive mitosis was occasionally observed. The sparse, mature neutrophils present revealed similar degenerative processes. The oxyphilic granulocytes were much better preserved but occasionally showed

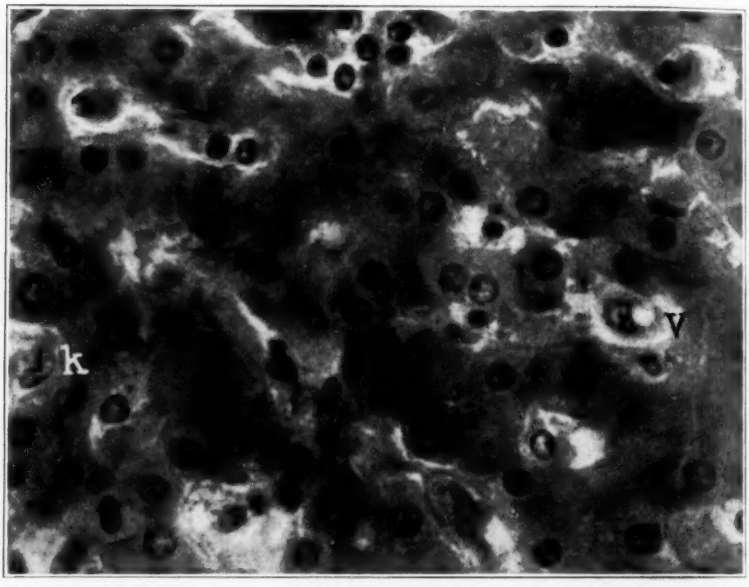

Fig. 4 (case 2).—Section of the liver (frozen) stained with hematoxylin and eosin. The Kupffer cells are conspicuous, chiefly because of swelling. The cytoplasm is increased in amount and is at times vacuolated (*v*). Some of the nuclei are the shape of a kidney bean (*k*). Many round histiocytic elements lie free in the lumens of the sinusoids. Magnification, × 600.

transformation of granules into droplets. The myeloblasts were intact. The nucleated red cells varied considerably in size. The majority of plasma cells were degenerated and had pyknotic nuclei. The megakaryocytes were greatly altered, their nuclei being shrunken and segmented and their granulation completely obscured. The differential count was as follows: myeloblasts 1 per cent, neutrophilic myelocytes 33.6 per cent, neutrophilic leukocytes 0.7 per cent, eosinophilic myelocytes 0.6 per cent, eosinophilic leukocytes 3.1 per cent, erythrogonia 2.8 per

cent, erythroblasts 12.7 per cent, normoblasts 36.6 per cent, lymphocytes 1 per cent, plasma cells 6.5 per cent, monocytoid cells 1 per cent, and megakaryocytes 0.4 per cent.

The connective tissue about the larger vessels of the heart was increased in amount, loose and edematous. It contained many swollen fibrocytes and loosely scattered lymphocytes and plasma cells. In the perivascular connective tissue were nodular accumulations of large cells with ample cytoplasm. Some of the nuclei of these cells showed the myocytic arrangement of the chromatin. Between these cells there was a varying number of small round cells, but no central area of fibrinoid necrosis was present. The muscle fibers were free from fat, and the cross-striations indistinct. There was considerable pigment at the poles of the nuclei. In the interstitial tissue were scattered, recent extravasations of blood.

The glomeruli of the kidneys were cellular, and the tufts often were plastered together and occasionally herniated in the openings of the tubules. Cells with oval or elongated nuclei predominated. The basal membrane was slightly thickened. Some of the glomeruli were completely, others partially, hyalinized. Here and there a crescent was observed in advanced fibrous transformation. Many of the convoluted tubules were filled by recent blood, others contained hemoglobin-tinted hyaline or waxy casts. A few glomeruli were associated with blood in Bowman's space. The tubular epithelium was often swollen and granular or contained hyaline droplets. An occasional tubule was lined by cells containing droplets of fat or iron granules. The stroma was slightly increased, especially about the hyalinized glomeruli. Some focal round cell infiltration was noted. The intima of the medium-sized arteries was moderately increased, whereas the walls of the arterioles were slightly thickened.

Bacteriologic Studies.—A culture of material from the spleen yielded a pure growth of Str. viridans.

Anatomic Diagnosis.—The diagnosis was sepsis lenta; huge tumor of the spleen with perisplenic adhesions; subacute glomerulonephritis; enlargement of the superficial and abdominal lymph nodes; petechial hemorrhages in the skin, peritoneum, kidneys, gastric mucosa and renal pelvis; irregular pigmentation of the skin of the lower extremities due to iron deposits in the cutis; ascites; brown atrophy of the heart; fibrous obliteration of the pericardial sac; fibrous obliteration of both pleural cavities; moderate passive congestion of the liver and lungs; fibrocalcareous subapical tuberculosis of the upper lobe of the left lung; focal bronchopneumonia of the lower lobe of the left lung; moderate emaciation; arthritis deformans of the hands; bilateral hallux valgus.

Case 2.—A white woman aged 49 entered the Cook County Hospital for the first time on July 1, 1932, because of symptoms referable to an acute cardiac decompensation. She stated that for at least five years previously she had suffered from arthritic manifestations involving principally the joints of the hands and knees. A week before entrance, while arising, she experienced precordial tightness and dyspnea. Edema of the feet followed. The constricting sensation and dyspnea increased in severity, and on this account she entered the hospital. Aside from arthritis, there was nothing of significance in her past history, except perhaps that she had influenza in 1918. There was no family history of rheumatic fever. She had borne no children. On physical examination the patient was found to be dyspneic and cyanotic. The blood pressure was 170 systolic and 110 diastolic. A systolic murmur was heard over the apex, and a gallop rhythm was detected. The liver was felt to extend 2 fingerbreadths below the costal margin. Nothing was recorded with regard to the size of the spleen. Dependent edema was noted.

There was deforming arthritis of the hands, the fingers being fixed in flexion at the metacarpophalangeal joints.

The patient rapidly improved under routine treatment for cardiac decompensation. During the early period of her confinement to bed, an irregular temperature was observed, frequently reaching 101 or 102 F. and persisting at that level for a few days at a time. The patient was allowed to be up on July 22 and was discharged on July 26 feeling well. She was home for a few days, when on August 5 pain was felt in the region of the right ear. A purulent discharge appeared two days later, and on August 11 the manifestations of erysipelas developed on the right side of the face. On this account the patient reentered the hospital on August 12 and remained for five days, at the end of which time the erysipelas had disappeared.

The patient returned to the hospital in a critical state on October 24. She related that after her discharge in August she had several attacks of shortness of breath and fainting. She had suffered also from attacks of vomiting, presumably due to digitalis which had been taken intermittently. Pallor, which was now quite apparent, had been noted by the patient for several months. The loss of weight during this time was approximately 30 pounds (13 Kg.). However, the patient was not confined to bed continuously until three days prior to the last admission, when a severe rigor occurred, followed by fever, sore throat and minor chills. Physical examination on admission disclosed an acutely ill white woman, very pale, dyspneic and toxic, with a temperature of 105.6 F., a pulse rate of 136 and a respiratory rate of 30. The skin and mucous membranes were tinted light yellow. Covering the tonsils and pharynx was a dirty yellowish-gray membrane which bled easily on manipulation. The anterior cervical lymph nodes were enlarged, especially on the right side. The heart was slightly enlarged to the left and over the apex a faint systolic blow was heard. The blood pressure was determined to be 170 systolic and 110 diastolic. Moist râles were heard over the bases of both lungs posteriorly, but no dulness could be demonstrated. The abdomen was tender in the left upper quadrant. The spleen was greatly enlarged to palpation. Deforming arthritis affecting the hands was also noted.

The initial diagnostic impression was agranulocytic angina. Examination of the blood showed an erythrocyte count of 1,480,000, a hemoglobin content of 35 per cent and a leukocyte count of 450. The differential count was: lymphocytes 81 per cent, monocytes 17 per cent, irritation forms 2 per cent and no granulocytes. No reticulocytes were encountered. The erythrocytes showed slight anisocytosis, poikilocytosis and an occasional polychromatophilic cell. A volumetric determination of the platelets showed 0.0006 per cent, equivalent to 42,000 platelets per cubic millimeter. The bleeding time was four and one-half minutes and the coagulation time eighteen minutes. Because of the depression of all the blood elements the diagnosis was revised to aplastic anemia. The presence of chills and fever suggested a septicemia as the cause of the aplastic blood picture. Blood which was drawn for culture revealed a pure growth of Str. viridans. Cultures of material from the throat and mucous membrane showed both Str. viridans and Str. haemolyticus. It was learned later that on Oct. 4, 1932, while the patient was under his care, Dr. H. C. Lueth obtained a pure growth of Str. viridans from the circulating blood. After frequent attacks of vomiting and a temperature varying from 104 to 106 F. the patient died two days following entrance. Necropsy was performed shortly after death by Dr. R. H. Jaffé.

Autopsy.—The salient features in the gross description can be briefly summarized. The microscopic changes in certain organs, however, require a detailed account.

Macroscopic Examination: There were moderate emaciation, marked pallor of the skin and mucous membranes and slight icteric discoloration of the conjunctivae. The superficial cervical lymph glands were moderately enlarged. Over the pharynx and covering the tonsils were necrotizing membranous deposits, beneath which were relatively clean ulcers. The fingers of both hands were fixed in a flexed position, and the joints were deformed by nodular swellings about the articular surfaces. The inguinal lymph glands were moderately enlarged and discrete. The spleen, which measured 6 by 12 by 22 cm. and weighed 620 Gm., extended 7 cm. below the costal arch in the anterior axillary line. It was moderately firm in consistency, and when sectioned the surface was found to be moist and light purple-gray, with light gray follicles measuring up to 1 mm. in diameter. On the posterior aspect near the upper pole there was a small, recent subcapsular anemic infarct. The liver weighed 1,950 Gm. and was moderately firm, smooth and purple-brown. The sectioned surfaces showed the acinar markings to be irregular. The heart weighed 365 Gm. The myocardium was light purple-brown and friable, and the valves of the heart were macroscopically unchanged. The lungs were moderately distended and subcrepitant, containing recent extravasations of blood. The kidneys were swollen and soft, and on the sectioned surfaces the cortical markings were obscured. There was a moderate swelling of the periaortic and peripancreatic lymph nodes, which were soft and purple-gray, and measured up to 1 by 1.5 by 3.5 cm. The bone marrow of the femur was soft and a light purple-gray.

Microscopic Examination: Only those organs or structures which demonstrated significant changes are included.

The sinuses of the spleen were wide and the lining endothelium only slightly prominent. The sinuses contained red blood cells, erythroblasts, normoblasts and a number of free histiocytes, each having a lobulated nucleus. The reticulum of the cords was markedly thickened, and its meshes contained small round cells, an increased number of plasma cells, a few nucleated red blood cells and an occasional megakaryocyte. The fibrillar hyperplasia was in striking contrast to the cellular hyperplasia of the reticulum as observed in case 1. The sinuses were sharply demarcated from the cords. The capsule and trabeculae were thickened. The lymph follicles were large and consisted only of lymphocytes. The reticular cells were slightly swollen. Underneath the capsule there was a wedge-shaped area which was completely necrotic and which was surrounded by a zone of marked congestion. Many of the sinuses in this region were filled by a dense net of fibrin.

The portal capillaries of the liver were diffusely dilated and filled by red blood cells, between which were clumps of platelets. There were moderate numbers of normoblasts and polychromatophilic erythroblasts. The Kupffer cells were prominent and possessed ample, occasionally vacuolated cytoplasm. Some of the Kupffer cells contained fat droplets. Free histiocytic elements, however, were relatively scanty. In the center and in the periphery of the acini, the liver cells contained small droplets of fat. The periportal tissue was densely infiltrated by lymphocytes, and between the lymphocytes were noted large mononuclear cells, the cytoplasm of which stained diffusely yellow.

The sinuses of the abdominal lymph nodes (periaortic and peripancreatic) were very much dilated and predominated over the lymphatic structures. The former were filled by erythrocytes and desquamated, large endothelial cells containing erythrocytes. The lymphatic tissue consisted of a mixture of lymphocytes, many plasma cells and a few large basophilic round cells. Secondary follicles were not visible. The reticular cells were markedly swollen.

The sinuses and capillaries of the bone marrow were dilated and congested. Most of the cellular elements were found outside the preformed blood spaces, in which only an occasional nucleated element could be detected. The reticular cells were swollen, and many of them contained engulfed red blood cells. The endothelium of the blood vessels was only moderately conspicuous. The cellularity of the bone marrow was 80 per cent, the fat tissue representing 20 per cent. The differential count gave the following figures and characteristics: There were 0.2 per cent myeloblasts and 2 per cent degenerated myelocytes. The myelocytic nucleus was usually fairly well preserved, but the cytoplasm appeared torn up or finely vacuolated. There was an occasional ill defined purple-pink granule or

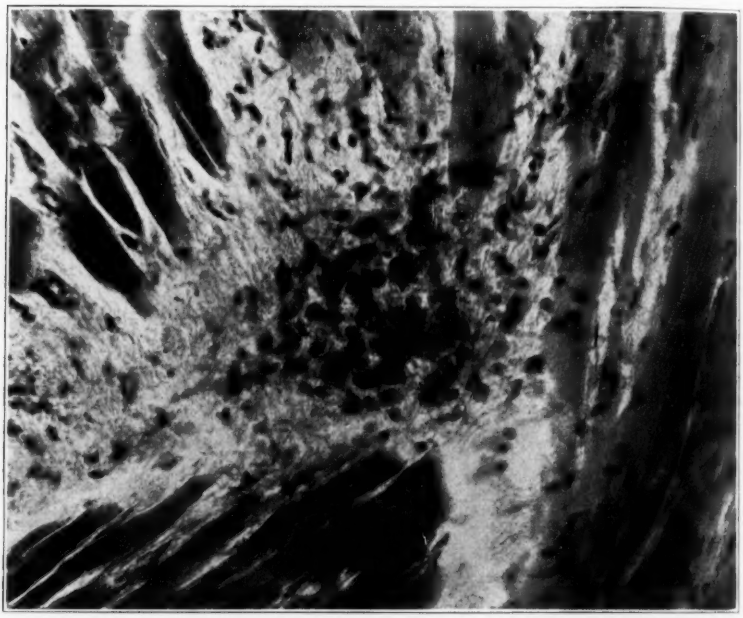

Fig. 5 (case 2).—Photomicrograph of a frozen section of a young, fan-shaped Aschoff body which is located in an intermuscular septum and composed of the typical cells with large nuclei. Under higher magnification the condensation of chromatin in the center of the nucleus is seen distinctly. The collagenic ground substance between the cellular elements of the nodule exhibits a fibrinoid swelling. There are edematous loosening and increased cellularity of the connective tissue comprising the septum. Hematoxylin and eosin stain; magnification, × 300.

droplet; a few of the myelocytes were necrotic. There were erythrogonia 4 per cent, erythroblasts 20 per cent and normoblasts 49.5 per cent. The normoblasts varied considerably in size, and some of them were large. There were 7 per cent lymphocytes, 3.6 per cent plasma cells, 5.6 per cent monocytoid cells and 2 per cent histiocytes. Many of the last cells contained erythrocytes. There were 2 per cent megakaryoblasts and 4 per cent megakaryocytes. The megakaryocytes

showed different stages of degeneration, and a few of them were necrotic; in the degenerated cells the cytoplasm was oxyphilic and free from granules. Many megakaryocytes contained erythrocytes or nucleated cell forms. In addition to the loosely scattered lymphocytes there were many well defined lymph follicles.

Fig. 6 (case 2).—Photomicrograph of a frozen section of a fully developed, spindle-shaped Aschoff body. Because of beginning regressive changes the characteristic condensation of the chromatin is not as pronounced as in figure 5. There is more fibrinoid material in this nodule than in the one pictured in figure 5. Hematoxylin and eosin stain; magnification, × 600.

In the subepicardial fat tissue of the myocardium many free mononuclear cells with ample cytoplasm were seen between the fat cells. There were small, focal accumulations of lymphocytes. An increased number of large free histiocytes

were also noted in the interstitial septums of the myocardium. In addition to these cells there were single nodular accumulations of large protoplasmatic cells with myocytic nuclei. The largest of these cells contained several nuclei. The cells were arranged about a pale, pink-stained fibrinoid center. These nodular accumulations exhibited the characteristic appearance of Aschoff bodies (figs. 5 and 6). The muscle fibers were fairly well preserved except for the presence of very small interstitial scars in which the muscle fibers were replaced by elongated cells containing light brown pigment granules. No change was present in sections of the leaflets of the mitral valve.

The glomeruli of the kidneys appeared large and cellular, and the blood content of the tufts was markedly diminished. Most of the cells in the tufts had elongated nuclei. Bowman's space was empty and was often obscured by the swollen tufts. The tubular epithelium showed granular swelling and in places a small amount of fat. There was marked diffuse capillary hyperemia, and the stroma was edematous. The intima of the medium-sized arteries was slightly thickened.

Bacteriologic Studies.—Cultures made post mortem yielded: (*a*) from the membrane and tonsillar area, a heavy growth of Str. viridans, and (*b*) from the spleen, both a green-producing streptococcus and a hemolyzing streptococcus.

Anatomic Diagnosis.—The diagnosis was: sepsis lenta; chronic tumor of the spleen with recent anemic infarct; cloudy swelling of the liver and the myocardium; Aschoff bodies in the myocardium; hyperplasia of the abdominal, cervical and inguinal lymph nodes; acute glomerulonephritis; pseudomembranous tonsillitis and pharyngitis; passive congestion and edema of the lungs; severe generalized anemia; subicteric discoloration of the skin and scleras; nodose goiter; deforming arthritis of the joints of both hands; hemorrhagic corpus luteum cyst.

COMMENT

In most of the cases of Felty's and related syndromes previously reported, the clinical manifestations were particularly emphasized. In a few instances isolated bacteriologic investigations were made post mortem and only occasionally during life. In instances in which necropsy observations were recorded, the data were generally restricted to gross alterations. If microscopic studies were made, the descriptions generally were inadequate. In no instance in the literature, so far as could be ascertained, are more or less complete clinical, bacteriologic and anatomic observations available. In both cases recorded the opportunity was afforded us of studying the patients clinically over a period of time, of making bacteriologic investigations during life and also post mortem and of examining the autopsy material in detail, both macroscopically and microscopically.

The first case reported here can be assumed from the clinical standpoint to be one of a chronic sepsis. In fact, the picture for several months was almost identical with that of subacute bacterial endocarditis. From the bacteriologic point of view the recovery of Str. viridans from the blood stream during life and from the spleen after death lends support to the clinical assumption. The anatomic changes, especially those

demonstrated by the microscopic examination, speak for a long-standing low grade infection, since they are typical of the alterations observed in sepsis lenta (Siegmund [57] and Jaffé [58]). These changes include activation of the endothelium, noted especially in the spleen, liver and lymph nodes and indicated by the swelling, increase in number and desquamation of the endothelial cells; erythrophagocytosis; distinct increase in the plasma cells in the spleen, lymph nodes and especially in the bone marrow; injury to the bone marrow elements and particularly the granulocytes; subacute glomerulonephritis; evidences of myocarditis, and hemorrhages into the cutis.

The considerations in the second case led to conclusions similar to those arrived at in connection with the first case. The existence of sepsis, although originally overlooked by the attending physicians, hardly could be questioned. Even during the patient's first stay in the hospital febrile periods were recorded. The bacteriologic observations likewise point to the presence of sepsis. They include the positive results from cultures of the blood for Str. viridans before and after the onset of severe symptoms; cultivation during life of green-producing and hemolytic streptococci from the membrane in the throat; a heavy growth of Str. viridans from the throat and tonsillar area after death; and isolation of green-producing and hemolytic streptococci from the spleen at necropsy (the hemolytic streptococci are considered secondary invaders). The morbid anatomy, especially the microscopic aspect, although differing somewhat from that of the first case, is also characteristic of sepsis lenta. Several features, however, warrant special comment.

In case 2 the reticulo-endothelial activation had apparently subsided, and in the spleen the fibrillar hyperplasia was seen to predominate over the cellular hyperplasia. These changes were older than those observed in case 1 and represent an advanced stage of the same pathologic process. Further differences between the two cases are explained on the basis of the extramedullary erythropoiesis, which occurred in the second patient as a result of the extreme injury to the bone marrow. The changes in the hematopoietic system with special reference to agranulocytosis have been dealt with elsewhere (Jaffé,[59] case 8). Of special interest were the typical Aschoff bodies observed in the myocardium. We do not wish at this time to enter into the vexed question of the histologic specificity of these nodes. Suffice it to say that our own

57. Siegmund, H.: Ueber einige Reaktionen der Gefässwände und des Endokards bei experimentellen und menschlichen Allgemeininfektionen, Verhandl. d. deutsch. path. Gesellsch. **20**:260, 1925.

58. Jaffé, R. H.: The Reticulo-Endothelial System, in Handbook of Hematology, edited by H. Downey, New York, Paul B. Hoeber, Inc., to be published.

59. Jaffé, R. H.: Bone Marrow in Agranulocytosis (Pernicious Leukopenia), Arch. Path. **16**:611 (Nov.) 1933.

observations lead us to believe with Clawson [60] and others that although characteristically noted in rheumatic fever the Aschoff nodule is not strictly limited to this condition. The specific response of the tissues rather than the type of invading organism is apparently the determining factor.

The evidence obtained in these two cases indicates that Felty's and related syndromes are special forms of sepsis lenta. The variations in the clinical picture and course can be readily explained by differences in the defensive response on the part of the individual tissues and the host as a whole. For instance, in case 1 of this report, it may be assumed that the infection was present for several years, during which time the patient's resistance was relatively high. In the last few months of his illness, however, the defense mechanism gradually became inadequate, and the sepsis progressed slowly until death. In the second case also the infection was of long standing. Here, however, a complete collapse of the protective mechanism occurred suddenly, whereupon the patient became rapidly overwhelmed by the sepsis and died a few days later. Whether a streptococcus and particularly one of the viridans type is the sole cause of Felty's and related syndromes is difficult to state. It can be stated, however, from the evidence at hand that the preponderance of bacteriologic evidence points to a green-producing streptococcus as the usual etiologic organism. In the light of the results reported in connection with studies on arthritis (Archer [61]), skepticism might be expressed in drawing conclusions based on bacteriologic observations alone. However, by inference, support can be adduced from other sources. It is universally accepted that subacute bacterial endocarditis is generally caused by Str. viridans. Since the morbid anatomy in our two cases is almost identical (except for the endocardial involvement) with that observed in Schottmüller-Libman's disease, a similar etiology seems quite plausible.

The evidence for assuming the presence of sepsis at the time of necropsy seems indisputable. However, the assumption that the disease begins as a septicemia due to the same organism years previously is open to question. Two observations lend support to the view that the disease from its inception is due to one and the same organism which is responsible for a single pathogenetic process. In the first place, the histologic changes observed at necropsy in our two cases are practically identical with those noted in cases of established sepsis lenta lasting over a period of several months or even years. In the second place the histologic picture of tissue, especially splenic tissue, removed from

60. Clawson, B. J.: The Aschoff Nodule, Arch. Path. **8**:664 (Oct.) 1929.

61. Archer, B. H.: Chronic Nonspecific Arthritis: Etiology and Treatment, with Special Reference to Vaccine Therapy, J. A. M. A. **102**:1449 (May 5) 1934.

patients who undergo surgical operation relatively early in the course of the disease (i. e., with reference to progression) resembles that in case 1 very closely. For example, in sections of the spleen removed at operation by Hanrahan and Miller the following changes were described: activation of the endothelial cells lining the sinuses; erythrophagocytosis, and increase in the number of plasma cells and probably in the number of reticulum cells of the pulp. These were the outstanding features noted in the spleen in case 1, and, indeed, an exchange of slides indicates that the process is probably an identical one (Hanrahan [62]). It will be remembered that splenectomy was performed by Hanrahan and Miller [2] at a time when the patient's general condition was comparatively good and the infectious process was practically stationary. In the case reported by Craven [4] the histologic description as well as the illustrations conform to the picture observed in case 1 and in the case reported by Hanrahan and Miller. Thus it is seen that the changes noted post mortem in our cases were similar to those observed in spleens removed at operation relatively early in the course of the illness. We feel inclined to believe, therefore, that the terminal picture in the cases recorded was not due to a superimposed infection but rather represented the end-stage of a single infection in which the defense mechanism of the host had collapsed.

SUMMARY AND CONCLUSIONS

A syndrome observed in adults comprising deforming arthritis, splenomegaly, lymphadenopathy, leukopenia and pigmentation was described in 1924 by Felty. This combination of symptoms has been observed since by other American writers who have applied the name of Felty's syndrome to the condition. In reviewing the world's literature one finds descriptions in European publications of cases in adults with similar clinical pictures referred to as instances of Chauffard's or Still-Chauffard's disease. The condition is generally thought to be the counterpart in adults of Still's disease in children.

A survey of the literature relating to the etiology of Felty's and associated syndromes yields a diversity of views, although a low grade sepsis is the cause favored by most writers. However, only a few disconnected bacteriologic and other observations have been adduced in support of this opinion. In two patients with the typical clinical picture of Felty's syndrome the opportunity presented itself for detailed study ante mortem as well as post mortem. In each instance the bacteriologic and anatomic evidence pointed to the presence of sepsis lenta.

On the basis of the data obtained in connection with the study of these two patients together with a review of the literature, it is believed that the several syndromes which include deforming arthritis and

62. Hanrahan, E. M., Jr.: Personal communication to the authors.

lymphadenopathy or splenomegaly represent different forms of the same disease. The underlying sepsis affects not only the joints but also the hematopoietic system, viz., the spleen, liver, bone marrow and lymph nodes. The variable response of the different tissues of the host determines the symptomatology and accounts for the different clinical pictures observed. The usual etiologic organism is believed to be a streptococcus of the viridans type. It is likely that other bacteria can occasionally produce Felty's and allied syndromes.

HOW ARTERIES COMPENSATE FOR OCCLUSION

AN ARTERIOGRAPHIC STUDY OF COLLATERAL CIRCULATION

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Nature is lavish in her methods of protecting an organism against harm. One of these methods is the production of tissue in excess of that which is needed for the normal function of an organ. The thyroid, parathyroid and adrenal glands, the kidneys, the pancreas, the testes and the ovaries are excessive, anatomically and functionally. Small amounts of these organs can function as units which are entirely adequate for normal demands.

Morgagni [1] made the first anatomic observations on the development of collateral circulation. These observations were added to by the experimental studies of John Hunter,[2] who ligated the main artery of the rapidly growing antler of a deer. The result was not a cessation of growth but rather a rapid appearance of many enlarged arteries, which carried the blood around the obstruction.[3]

It is not surprising that the arterial circulation is equipped with safeguards. The integrity of a limb depends on the arterial circulation to the extent that the limb cannot survive marked deficiency of the arterial circulation. The relation of some of these safeguards is the purpose of this paper. Patients who were afflicted with thrombo-angiitis obliterans were studied.

THE TECHNIC OF ARTERIOGRAPHY

Roentgenologic visualization of the peripheral arteries of living subjects has become a commonplace procedure. Briefly stated, the method consists of the injection of an opaque substance and exposure of a roentgenographic film under the extremity to the roentgen rays while the opaque medium is in the arteries. The exact technic, value and uses of arteriography and the substances which are used for intra-arterial injection have been reviewed elsewhere.[4]

From the Division of Medicine, The Mayo Clinic.

1. Morgagni, quoted by Mulvihill and Harvey.[3]

2. Hunter, John, quoted by Mulvihill and Harvey.[3]

3. Mulvihill, D. A., and Harvey, S. C.: The Mechanism of the Development of Collateral Circulation, New England J. Med. **204**:1032 (May 14) 1931.

4. Allen, E. V., and Camp, J. D.: Arteriography: A Roentgenographic Study of the Peripheral Arteries of the Living Subject Following Their Injection with a Radiopaque Substance, J. A. M. A. **104**:618 (Feb. 23) 1935.

THE NORMAL ARTERIOGRAM

The roentgenographic appearance of normal arteries is characteristic.[4] From the forearm the radial and ulnar arteries proceed to the hand, where they form the palmar arches. The interosseous arteries usually end in branches proximal to the wrist, but occasionally they pass into the hand. The digital arteries arise from the palmar arches and bifurcate at the approximate level of the metocarpophalangeal joints to course along the lateral surfaces of the digits. In the forearm and hand rather numerous fine short branches may be seen. In the fingers fewer branches are seen. Not infrequently small branches of the ulnar or radial arteries may be seen, which arise proximal to the level of the wrist and run distally to the hand.

THE COLLATERAL CIRCULATION

The term collateral is used in this study to indicate arteries and evidence of circulation in arteries which ordinarily are not seen in roentgenograms of the extremities of persons who do not have arterial disease. One who studies arteriograms of patients with occlusive arterial disease cannot avoid being impressed with the marvelous capacity of the circulation to compensate for the occlusion of arteries. It is obviously this compensatory or collateral circulation which prevents gangrene in many cases of occlusive arterial disease. It also follows that restoration of a rather normal arterial circulation in cases in which there is chronic arterial occlusion depends on the establishment of collateral circulation.

The chief characteristics of collateral arteries are the irregular, turning and twisting course which they pursue; their variation in size in any selected area; their apparent purposeless crossing and recrossing; their lateral course in areas in which they are profuse, and their anastomosis (fig. 1). These arteries are in contrast to normal arteries, which pursue a direct and largely longitudinal course, with a minimum of crossing, which are more constant in size in any specific area and which manifest a minimum of anastomosis with each other.

METHODS OF ESTABLISHING COLLATERAL CIRCULATION

Anastomosis.—When an artery is partially occluded a large collateral branch may arise from it above the point of occlusion. The collateral artery passes at right angles to the parent artery for a short but variable distance and then turns abruptly to run roughly parallel to the course of the diseased artery. Distal to the point of occlusion it turns sharply and joins the parent artery at right angles (fig. 2*A*). When occlusion of the diseased artery is complete the collateral artery carries the blood around the occlusion in a fairly adequate manner, as shown

by normal filling of the artery distal to the point of its occlusion (fig. 2*B*). I have never observed anastomosis of two main parallel arteries in the arteriogram of a normal person. It occurs infrequently, but occasionally, in cases of thrombo-angiitis obliterans. Direct communications have been observed between the interosseous and the radial arteries and between the interosseous and the ulnar arteries (fig. 2*C*).

Fig. 1.—A collateral artery characterized by a turning and twisting course.

Lateral Branching.—Occlusion of a digital artery with minimal involvement of its companion artery is frequently seen. In such instances the artery which is not diseased sends numerous branches laterally to the site of the diseased artery. These collateral arteries are numerous and seem to supply the tissues which have been deprived of their normal blood supply in an adequate manner. Some of them may join unoccluded portions of the diseased artery to form cross-anastomoses (fig. 3). Lateral branching from the unoccluded portion of an

artery may compensate for occlusion of a companion artery. I have observed that a branch of the radial artery may cross to the ulnar side of the wrist when the ulnar artery is occluded (fig. 2 *C*).

Prolongation.—Ordinarily, the interosseous arteries do not extend beyond the wrist. When the radial and ulnar arteries are occluded

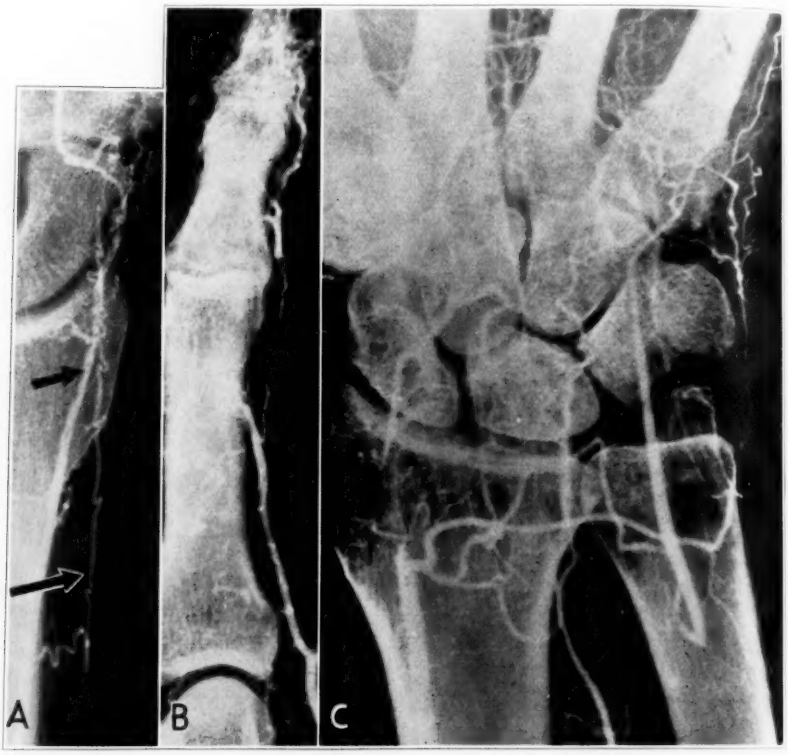

Fig. 2.—Collateral circulation by anastomosis. In *A* the distal arrow indicates partial occlusion of a radial artery. The proximal arrow indicates a collateral artery which joins the radial artery distal and proximal to the area of partial occlusion. In *B* a small collateral artery connects portions of the digital artery distal and proximal to the area of occlusion. In *C*, showing collateral circulation by lateral branching, the ulnar artery has been occluded proximally. A collateral branch passes from the radial artery to the ulnar side of the wrist. The interosseous artery is connected with the radial and ulnar arteries by direct anastomosis.

above this level, the branches of the interosseous arteries invariably extend down to the hand. The branches arise from the distal end of the interosseous arteries and extend out to both the radial and the ulnar

side of the wrist as well as distally to join with collateral arteries in the hand (fig. 4). This is a fortunate provision because, in my experience, the interosseous arteries are almost never occluded. It possibly explains why gangrene of the foot is not uncommon in cases of thromboangiitis obliterans, while gangrene of the hand never occurs.

Terminal Branching.—When an artery is occluded throughout a considerable portion of its course, numerous branches may arise from above

Fig. 3.—Collateral circulation by lateral branching. The digital artery on the left has been occluded segmentally. Many collateral branches pass laterally from the digital artery on the right.

the area of occlusion and pass distally in a direction roughly parallel to that of the diseased artery. In a case of occlusion of the middle and distal thirds of the femoral artery and of the popliteal artery, large collateral branches, which arose from the unoccluded portion of the femoral artery, were observed to pass to a level well below the knee.

The Network of Collateral Arteries.—In some cases in which occlusion of the normal arteries has been extensive, particularly in the palm, the arteries are represented by an irregular network of crossing branches, the origin, direction and termination of which are difficult or impossible to determine (fig. 5). It is probable that in this confusing network of collateral arteries all the methods for establishing collateral arteries, which have been described previously, are utilized.

Fig. 4.—Collateral circulation by prolongation. The radial and ulnar arteries are occluded. The interosseous artery extends distally into the hand and sends branches to the radial and ulnar sides of wrist.

COMMENT

It is obvious from this study that collateral circulation is profuse in cases of occlusive arterial disease. Logical and purposeful design in the development of collateral circulation is apparent, for without the

ability to develop collateral circulation the integrity of limbs would be seriously endangered by comparatively minor degrees of arterial occlusion. It is of interest that the methods by which embarrassment of the circulation results from arterial occlusion is overcome in the extremity are about the same as those which an engineer would use to surmount similar obstacles in hydrodynamics. If a segment of a stream was occluded by a dam which could not be removed, what would be more

Fig. 5.—Collateral circulation by network formation. The normal arteries in the hand have been occluded. Circulation is maintained by a network of arteries.

logical than the construction of a canal around the dam, thus reestablishing the continuity of the stream (fig. 2 *A* and *B*)? Or if one of two parallel canals was irremediably destroyed, how could the problem be better solved than by sending branches out laterally from the unoccluded canal to the area which ordinarily was supplied by the one which was destroyed (fig. 3)? For every method of overcoming arterial occlusion, as seen in the arteriogram, there exists a logical parallel procedure to overcome a similar obstacle in hydrodynamics.

Neither this observation nor Hunter's statement that "the blood goes where it is needed" satisfactorily answers questions about the origin of collateral circulation.[3] How do collateral arteries develop? Are they constructed anatomically in situ, or do they represent increased function in arteries which already exist? A somewhat analogous situation exists in the glomeruli of the kidney; only a small percentage of these function at any one time.

Contrast of the arteriograms of normal limbs of the living subject with the arteriograms of limbs which have been amputated for reasons other than arterial disease [5] reveals marked differences. In the latter condition the number of arterial branches and the surface area which is occupied by the arteries are much greater than those which are seen in arteriograms of normal living subjects. This is evidence that a great many arterial branches which are not visible in the arteriogram of living subjects exist nevertheless. This failure to render many existing arteries visible in the arteriograms of living subjects is apparently not a defect of the method; these arteries apparently are not functioning. Further evidence for this assumption is offered by the experimental work of Horton and Craig,[6] who made arteriograms of the hindlegs of dogs, on some of which sympathectomy had been performed. The surface area which was occupied by arteries was much greater in the limbs in which sympathetic denervation had been performed than it was in the normal control limbs. It is a common observation that blocking of the sympathetic impulses to an extremity by anesthesia or by operation leads to an immediate and sharp increase in the temperature of the part, a manifestation of increased circulation. This is almost certain evidence of increased function of the arteries, which existed in a partial or complete resting state before the interruption of the sympathetic impulses was effected.

Mulvihill and Harvey [3] have demonstrated that after ligation of the external iliac artery the temperature of the leg of a dog drops rapidly to the level of the temperature of the room. After a few hours the temperature rises rather abruptly to that of the control limb. Further experiments demonstrated that if sympathectomy was performed before ligation of the artery no decrease in the temperature occurred when ligation was performed, and if sympathectomy was performed when the temperature was low, as a result of ligation of the artery, the extremity immediately became as warm as the normal member. These experi-

5. Horton, B. T.: A Study of the Vessels of the Extremities by the Injection of Mercury, S. Clin. North America **10**:159 (Feb.) 1930.

6. Horton, B. T., and Craig, W. McK.: Evidence Shown in the Roentgenograms of Changes in the Vascular Tree Following Experimental Sympathetic Ganglionectomy, Arch. Surg. **21**:698 (Oct.) 1930.

ents offer convincing evidence of the major rôle of the vasomotor component in establishing collateral circulation, and when considered with other data which have been presented briefly in the preceding paragraphs, they indicate that, in the main, collateral arteries which are seen in the arteriograms of living subjects who have thrombo-angiitis obliterans are arteries which were present before the onset of the arterial disease. The function and hence the size of these arteries was increased, apparently to compensate for occlusion in the main arteries.

SUMMARY

Collateral circulation may be very profuse in cases of thrombo-angiitis obliterans. By methods which have been designated as anastomosis, lateral projection, prolongation, terminal branching and network formation, a collateral circulation develops which can compensate for extensive occlusion of the chief arteries of an extremity. There is indirect but entirely logical and convincing evidence that collateral arteries are chiefly arteries which are present normally but which have increased in size as a response to a demand for increased function which arises as a result of occlusion of the main arteries.

PNEUMOTHORAX THERAPY IN EXPERIMENTAL LOBAR PNEUMONIA IN THE DOG

WITH A REPORT OF A CASE IN MAN

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The treatment of lobar pneumonia, both experimental and clinical, with artificial pneumothorax has lately been revived with enthusiasm. The present studies were undertaken to see whether we could corroborate the success reported with the use of pneumothorax in the treatment of experimental lobar pneumonia in the dog.

EXPERIMENTAL PROCEDURE

Healthy dogs weighing from 8 to 12 Kg. were used.

Pneumococcus.—The method first devised by Coryllos and Birnbaum[1] was used. From 20 to 30 cc. of an eighteen to twenty-two hour broth culture of Pneumococcus type I, II or III was centrifugated, and the sediment was suspended in 1 cc. of the supernatant broth. The suspension was then sprayed by gentle air pressure through a 2 mm. brass tube over the mouth of the bronchus of the lower lobe. The bronchoscope was used to locate the bronchus. In some cases the sediment was suspended in liquefied 1.5 per cent agar broth instead of in plain nutrient broth and injected into the bronchus. After insufflation of the culture the bronchoscope was removed, and the animal was placed on its right side in a warm room till the return of consciousness.

Anesthesia.—An injection of 55 milligrams of amytal (iso-amylethyl barbituric acid) per kilogram of body weight in the form of a 10 per cent solution of sodium amytal was given intraperitoneally.

Pneumothorax.—From 200 to 350 cc. of air was injected under manometric control, usually in the fifth interspace in the postaxillary line.

Blood Cultures.—Approximately twenty-four hours after the culture of Pneumococcus was insufflated into the lung, 2 cc. of blood was drawn from the vein of the leg under sterile precautions for culture on plates of poured agar broth. With a few exceptions, the blood from the heart was cultured at autopsy. In our tables the reports on the cultures of the blood taken after twenty-four hours and those on cultures of the blood from the heart taken at autopsy are differentiated. When either culture was positive it was stated in the tables of analysis that the animal had bacteremia.

From the Department of Surgical Research, Cornell University Medical College. This work was aided by a gift from Mrs. John L. Given in support of surgical research.

1. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia Considered as a Pneumococcic Lobar Atelectasis of the Lung: Bronchoscopic Investigation, Arch. Surg. **18**:190 (Jan.) 1929.

ANALYSIS OF EXPERIMENTAL DATA

Forty animals were used in the experiment. Table 1 presents a general summary. It will be noted that there were three moribund dogs in the whole series, two in the group of untreated (control) animals and one in the group of dogs receiving pneumothorax. By "moribund" we mean comatose; nearly always subnormal temperature accompanied the coma. All three moribund dogs had bacteremia and succumbed. In four animals which died, the lungs were normal at autopsy; two (dogs 35 and 41) had received pneumothorax, and two (dogs 60 and 62) had not.

Of the first two animals, which were ailing until they died, in fifty-six and fifty-seven days, respectively, one had bacteremia at the start of the illness and at death; the other had no bacteremia at the beginning or at death. Both the other two animals (dogs 60 and 62) in the group of controls appeared clinically well on the fourth day, but they were found dead, one on the thirty-fifth and one on the thirty-eighth day; both had had bacteremia. All four deaths were classed as due to experimental factors. Still another animal in the group of controls (dog 56) appeared clinically well on the fourth day but was found dead on the twenty-sixth day; this animal had bacteremia at the start. The autopsy revealed pathologic changes due to pneumococcus in the lower and middle lobes of the right lung. One animal (dog 55) in the group receiving pneumothorax appeared well at the end of six days but was found dead on the one hundred and twelfth day; although the dog had had bacteremia at the start the outcome was recorded as recovery from experimental pneumonia with the use of pneumothorax, the cause of death not being revealed at autopsy.

For the sake of brevity in the analysis, the term "toxic" is used to indicate toxicity of a moderate or high degree or moribundity (tables 3 to 8). It will be noted that fifteen of the seventeen animals given pneumothorax were very sick (group of toxic animals), one of these being moribund. Of the remaining twenty-three dogs, which did not receive pneumothorax, only eleven were very sick, two of which were moribund. For this reason, analyses were made of data on animals with a comparable degree of toxicity, as the tables show.

Tables 2 to 10 reveal the following facts:

1. For the total number of forty animals, the incidence of bacteremia was 37 per cent and the mortality 37 per cent.

2. For the fourteen animals showing little or no toxicity, the incidence of bacteremia was 14 per cent and the mortality 7 per cent. The twelve animals in this group which did not receive pneumothorax recovered.

TABLE 1.—*General Summary of Experimental Data on Forty Dogs in Which Lobar Pneumonia Was Induced with the Results of Pneumothorax Therapy*

Dog	Weight, Kg.	Volume of Sedimented Pneumococci Suspended in Broth, Cc.	Type of Pneumococcus	Lobe of Right Lung in Which Pneumonia Was Induced in 24 Hrs.	Degree of Clinical Toxicity	Clinical Course	Results of Blood Culture	Observations 24 Hours After Insufflation: Temperature, C.	Pulse Rate	Respiratory Rate	Volume of Pneumothorax, Cc.	Postmortem Observations	Comment
1,001	10	0.05	I	Lower	Slight	Very well 2 days after culture was given; recovery	Negative	39.2 (102.6 F.)	90	40	...	....	.....
1,002	10.5	0.05	I	Lower	None	Very well; recovery	Negative	39.4 (102.9 F.)	100	35	...	.....	.....
1,003	10.5	0.5	I	Lower, middle ?	Moderate to high	Slight improvement 2 days after culture was given; recovery	Negative	39.2 (102.6 F.)	100	30	250	.....	After pneumothorax pulse rate rose to 120, respirations to 60 (shallow); 2 days after first pneumothorax temperature 39.6 C. (103.3 F.), pulse 90, respirations 40
1,004	10	0.05	I	Lower	Moribund	Coma; death 24 hrs. after pneumothorax	1 colony on plate; heart blood 200 colonies	36.1 (96.98 F.)	80	30	300	In right lung, lower lobe and half of upper showing gray consolidation; slight amount of serosanguineous fluid in both pleural cavities	After pneumothorax respiratory rate rose from 30 to 50; death in 24 hours after pneumothorax; coma
1,006	10	0.05	II	Lower	Very high	Very well 2 days after culture was given; recovery	Negative	39.6 (103.3 F.)	150	50	250 250	.....	After pneumothorax respiratory rate rose from 50 to 60; 2 days after first pneumothorax, temperature 39.4 C. (102.9 F.), pulse 95, respirations 40
1,005	10	0.05	II	Lower	Slight	Very well 2 days after culture was given; recovery							
1,007	10	0.05	II	Lower	None	Very well; recovery	3 colonies on plate	38.4 (101.1 F.)	100	26	...	....	.....
1,008	10	0.05	I	All	Very high	Moderately ill; respiration labored 3 days after culture was given; recovery	Negative	38.6 (101.5 F.)	150	60	250 350	.....	After first pneumothorax respirations rose from 60 to 70; 3 days after first pneumothorax, temperature 39.2 C. (102.6 F.), pulse 100, respirations 60 (grunting respiration)
1,011	6	0.035	I	Lower	Slight	Very well 2 days after culture was given; recovery	Negative	39.0 (102.2 F.)	110	56	...	....	.....

1,012	10	0.06	I	Lower	Slight	Very well 2 days after culture was given; recovery	Negative	40.0 (106 F.)	95	65	....	.....	.....
1,013	12	0.07	I	All	Moribund	Coma; death 24 hrs. after culture was given	Heart blood 1 colony on plate	36.0 (96.8 F.)	90	60	....	.....	.....
1,014	14	0.07	I	Lower	Very high	Much improved 2 days after culture was given	Negative	39.6 (103 F.)	100	40	....	.....	.....
1,020	10	0.06	I	Lower, middle	Very high	Very well 4 days after culture was given	Negative	....	....	.	300	.....	Showed considerable resistance before pneumothorax; staggering around room
1,023	10	0.05	I	Lower	Very high	Very well 2 days after culture was given; recovery	Negative	....	....	..	....	.....	.....
1,024	10	0.05	I	Lower	None	Very well; recovery	Negative	....	....	..	....	.....	.....
1,026	10	0.05	I	Lower	Very high	Much improved 2 days after culture was given; recovery	Negative	....	....	..	200 300	.....	.....
1,025	10	....	..	Lower	Slight	Very well; recovery	Negative	....	....	..	....	.....	.....
1,033	10	0.05	I	Lower	Slight	Very well 2 days after culture was given; recovery	Negative	....	....	..	....	.....	.....
1,034	10	0.05	I	Lower, middle ?	Moderately high	Improved 2 days after culture was given; recovery	Negative	....	....	..	300 275	.....	.....
1,035	8	0.07	I	Lower	Very high	Improved 2 days and worse 3 days after culture was given; ailing until death on fifty-seventh day	2 colonies in 48 hrs.; 60 colonies heart blood	39.3 (102.7 F.)	120	40	250 300	Lungs normal	.....
1,036	8	0.07	I	Lower	None	Very well; recovery	Negative	....	....	..	....	.....	.....
1,037	8	0.07	I	Lower	Very high	Very well 2 days after culture was given; recovery	Negative	39.4 (102.9 F.)	100	50	....	.....	.....
1,038	10	0.07	I	Lower	None	Very well; recovery	Negative	....	....	..	....	.....	.....
1,039	10	0.05	III	Lower, middle ?	Very high	Much improved 3 days after culture was given; recovery	1 colony in 48 hrs.	39.4 (102.9 F.)	100	60	....	.....	.....
1,040	10	0.05	III	Lower, middle	Slight	Quite ill on third day; improved 5 days after culture was given; recovery	Negative	39.8 (103.6 F.)	100	40	....	.....	.....
1,041	10	....	III	Lower, middle	Very high	Improved on second day; worse third day after culture was given; ailing until death on fifty-sixth day	Negative; heart blood negative (taken at death)	39.4 (102.9 F.)	100	60	325 325	Lungs normal	Respiration labored after each pneumothorax; 6 days after pneumothorax expiratory grunt; temperature 41 C. (105.8 F.), pulse 90, respirations 34

TABLE 1.—*General Summary of Experimental Data on Forty Dogs in Which Lobar Pneumonia Was Induced with the Results of Pneumothorax Therapy—Continued*

Dog	Weight, Kg.	Volume of Sedimented Pneumococci Suspended in Broth, Cc.	Type of Pneumococcus	Lobe of Right Lung in Which Pneumonia Was Induced in 24 Hrs.	Degree of Clinical Toxicity	Clinical Course	Results of Blood Culture	Observations 24 Hours After Insufflation: Temperature, C.	Pulse Rate	Respiratory Rate	Volume of Pneumothorax, Cc.	Postmortem Observations	Comment
1,042	10	0.05	III	Lower	Slight	Improved in 2 days and worse 3 days after culture was given; clinically well on seventh day; recovery	Negative	39.6 (103.3 F.)	110	50	200 275	.....	Pneumothorax given on second and third days after culture; respiration increased after each treatment; expiring grunt persisted after second pneumothorax; 5 days after first pneumothorax, temperature 38.9 C. (102.2 F.), pulse 95, respirations 50
1,045	8	0.05	III	Lower, middle ?	Moderately high	Improved 2 days after culture was given; recovery	Negative	40.4 (104.7 F.)	100	40	...	.....	.....
1,046	8	0.05	III	Lower	Moderately high	No improvement; death 7 days after use of pneumothorax was started	Negative	39.6 (103.3 F.)	120	40	300 300	In right lung, lower lobe with gray hepatization; upper and middle atelectatic	Dyspnea after each pneumothorax; day after first pneumothorax temperature 40 C., pulse 95, respirations 50; 4 days after pneumothorax was started temperature 40.1 C., pulse 95, respirations, 45
1,047	8	0.05	III	Lower	Slight	Worse 2 days and slightly better 3 days after culture was given; death 8 days after pneumothorax was started	Negative; heart blood 200 colonies	41.0 (105.8 F.)	100	40	300 200	Accessory lobe of lower lobe of right lung in stage of red hepatization	After first pneumothorax respiratory rate rose from 40 to 50; day after first pneumothorax temperature 40 C. (106 F.), pulse 120, respirations 60; dog more ill 4 days after first pneumothorax; temperature 39.8 C. (103.5 F.), pulse 100, respirations 40
1,048	10	0.06	III	Lower, middle	Moribund	Coma; improved in 2 days and better in 3 days after culture was given	1 colony in 48 hrs.	39.8 (103.6 F.)	120	45	...	Red hepatization in lower middle accessory and half of the upper lobes of the right lung	.....
1,051	8	0.06 in 1.5% agar broth	III	.....	Very high	Extreme toxicity continued; death 48 hours after culture was given	4 colonies in 48 hrs.	36.1 (96.9 F.)	100	60	250	All lobes of right lung consolidated; reddish gray	.....

								39.8	100	40	...	Lower half of upper	Blood from rectum 5 days

1,052	8	0.06 in 1.5% agar broth	III	Upper	Very high	Improved in 2 days; died 7 days after culture was given	Negative	39.8 (103.6 F.)	100	40	...	Lower half of upper and accessory lobes of right lung consolidated; fluid over pyriform sinuses; vomitus in mouth; asphyxia?	Blood from rectum 5 days before death
1,055	9	0.045 in 1.5% agar broth	III	Lower, middle?	Very high	Very ill on second and third days after culture was given; appeared well after 6 days; died in 112 days; reported as clinical recovery	3 colonies in 4 days	39.6 (103.3 F.)	90	60	325 300	Lungs, heart and abdomen generally involved	Marked dyspnea after each pneumothorax; on day after second pneumothorax dog very sick with dyspnea; temperature 40.5 C. (104.9 F.), pulse 60, respirations 60; 6 days after first pneumothorax appeared well, but temperature was 39.7 C. (103.1 F.), pulse 90, respirations, 50; classed as clinical recovery
1,057	10	0.05 in 1.5% agar broth	III	Lower	Very high	No improvement on second and third days after culture was given or until death 10 days after production pneumothorax started	Negative 4 days; heart blood 60 colonies	40.9 (106 F.)	100	55	325 225	Lower lobe of right lung gray-pink; organization	Marked dyspnea after each pneumothorax; on day after second pneumothorax, temperature 39.8 C. (103.6 F.), pulse 95, respirations 50, and 6 days after first, temperature 39.4 C. (102.4 F.), pulse 80, respirations 40
1,056	11	0.05 in 1.5% agar broth	III	Lower	Very high	Appearance good 7 days after culture was given though temperature, pulse rate and respiratory rate were 39.4 C. (102.9 F.), 90 and 46, respectively; found dead on twenty-sixth day	25 colonies in 4 days	40.2 (104.6 F.)	95	60	...	Lower half of lower lobe of right lung purulent, gray and partly organized; lobe of right middle lung consolidated and pinkish-gray	Death classed as due to experimental factors
1,059	9	0.06 in 1.5% agar broth	III	Lower, middle?	Very high	Died 30 hours after culture was given and 7 hours after pneumothorax	3 colonies in 48 hrs.; heart blood 12 colonies in 72 hrs.	36.8 (98.2 F.)	90	70	275	All lobes of right lung with red hepatization	Marked dyspnea after pneumothorax
1,060	11	0.065 in 1.5% agar broth	III	Lower	Very high	Very well after 2 days; clinical recovery in 4 days; died in 35 days	3 colonies in 48 hrs.	39.4 (102.4 F.)	100	60	..	Lungs normal; cause of death unknown	Death classed as due to experimental factors
1,061	11	0.065 in 1.5% agar broth	III	Lower, middle	Very high	Very well after second pneumothorax; improved 3 days after second pneumothorax and died on this day in convulsion	1 colony in 48 hrs.; heart blood 60 colonies	40.4 (104.7 F.)	100	60	275 275	Lower and accessory lobes of right lung with gray hepatization; upper and middle lobes atelectatic; ruptured abscess in lower lobe of right lung not related to pneumothorax	Marked dyspnea; rapid respiration for 1 day after each pneumothorax, spontaneous pneumothorax and asphyxia?
1,062	11	0.065 in 1.5% agar broth	III	Lower	Moderately high	Much improved after 2 days; very well on fourth day; died in 38 days	1 colony in 48 hrs.	40.4 (104.7 F.)	90	50	...	Lungs normal; cause of death unknown	Death classed as due to experimental factors

TABLE 2.—*Relation of the Incidence of Bacteremia to the Incidence of Death (Total Group)*

		Dogs Which Died		Dogs Which Recovered	
	Number	Number	Percentage	Number	Percentage
Total number of dogs	40				
Dogs with negative blood cultures	25	3	12	22	88
Dogs with positive blood cultures	15	12	80	3	20
Incidence of bacteremia, 37 per cent					
Incidence of death, 37 per cent					

TABLE 3.—*Relation of the Incidence of Bacteremia to the Incidence of Death (Group of Toxic Animals)*

		Dogs Which Died		Dogs Which Recovered	
	Number	Number	Percentage	Number	Percentage
Dogs showing toxicity	26				
Dogs with negative blood cultures	12	2	17	10	83
Dogs with positive blood cultures	14	12	86	2	14
Incidence of bacteremia, 54 per cent					
Incidence of death, 54 per cent					

TABLE 4.—*Relation of the Incidence of Bacteremia to the Incidence of Death for Groups of Dogs Not Treated with Pneumothorax and for Groups of Treated Dogs*

		Dogs Which Recovered		Dogs Which Died	
	Number	Number	Percentage	Number	Percentage
Dogs treated with pneumothorax	15				
Dogs with positive blood cultures	8	1	13	7	87
Dogs with negative blood cultures	7	5	71	2	29
Dogs not treated with pneumothorax	11				
Dogs with positive blood cultures	6	1	17	5	83
Dogs with negative blood cultures	5	4	80	1	20

TABLE 5.—*Relation of the Incidence of Bacteremia to the Incidence of Death for Groups of Dogs Not Treated with Pneumothorax and for Groups of Treated Dogs (Analysis 2)*

		Dogs With Bacteremia	
	Number	Number	Percentage
Animals showing toxicity	26		
Dogs treated with pneumothorax	15		
Dogs which died	9	7	78
Dogs which recovered	6	7	17
Dogs not treated with pneumothorax	11		
Dogs which died	6	5	83
Dogs which recovered	5	1	20

TABLE 6.—*Relation of the Incidence of Recovery for Dogs Not Treated with Pneumothorax to the Incidence for Treated Dogs, Irrespective of Bacteremia*

		Dogs Which Died		Dogs Which Recovered	
	Number	Number	Percentage	Number	Percentage
Animals showing toxicity	26				
Dogs treated with pneumothorax	15	9	60	6	40
Dogs not treated with pneumothorax	11	6	55	5	45

TABLE 7.—*Relation of the Incidence of a High Degree of Toxicity for Animals Not Treated with Pneumothorax and That for Treated Animals*

	Number	Dogs Which Were Moribund and Highly Toxic	Dogs Which Were Moderately Toxic	Ratio of the Degrees of Toxicity
Animals showing toxicity	26			
Animals treated with pneumothorax	15	12	3	4:1
Animals not treated with pneumothorax	11	9	2	4.5:1

TABLE 8.—*Comparison of Changes in the Indications of Toxicity on the Third Day After Insufflation of Pneumococcus for Dogs Not Treated with Pneumothorax and Those for Treated Dogs*

		Dogs Appearing Worse or Unimproved	
	Number	Number	Percentage
Dogs showing toxicity	26		
Dogs treated with pneumothorax	15	9	60
Dogs not treated with pneumothorax	11	3	37

TABLE 9.—*Relation of the Incidence of Bacteremia and the Incidence of Death for a Group of Nontoxic Animals, Irrespective of Treatment with Pneumothorax*

	Total Number	Number of Dogs Which Died	Number of Dogs Which Recovered
Dogs slightly or not toxic	14		
Dogs with bacteremia	2	1	1
Dogs without bacteremia	12	0	12

Incidence of bacteremia, 14 per cent
Incidence of death, 7 per cent

TABLE 10.—*Relation of Treatment with Pneumothorax to the Incidence of Bacteremia and the Incidence of Recovery for a Group of Nontoxic Animals*

	Total Number	Number of Dogs Which Died	Number of Dogs Which Recovered
Dogs slightly or not toxic	14		
Dogs treated with pneumothorax	2		
Dogs with bacteremia	1	1	0
Dogs without bacteremia	1	0	1
Dogs not treated with pneumothorax	12		
Dogs with bacteremia	1	0	1
Dogs without bacteremia	11	0	11

3. For the twenty-six toxic animals the following data were obtained:

(*a*) The incidence of bacteremia was 54 per cent and the mortality 54 per cent.

(*b*) Sixty per cent of the dogs receiving pneumothorax and 55 per cent of the dogs not receiving pneumothorax died.

(*c*) Eighty-six per cent of the dogs with bacteremia and only 17 per cent of the dogs without bacteremia died.

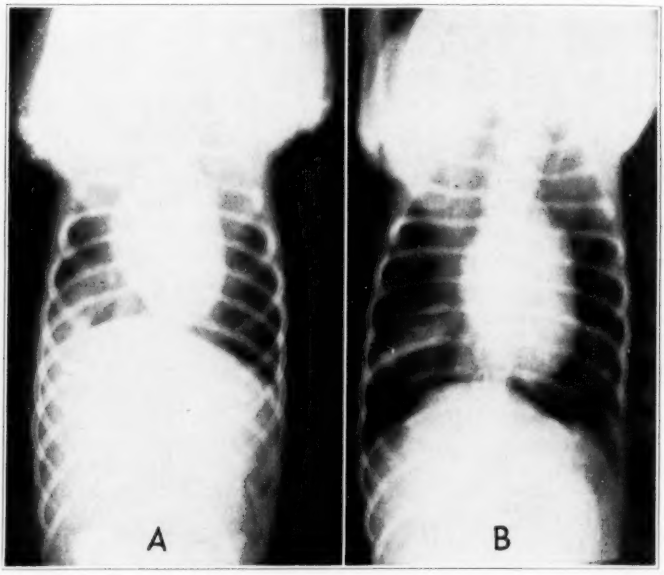

Fig. 1 (dog 35).—Roentgenograms of the lungs, showing (*A*) pneumonia of twenty-four hours' duration in the lower lobe of the right lung and (*B*) the appearance after the production of pneumothorax on the right side with 350 cc. of air. Bilateral pneumothorax is evident.

(*d*) Of the dogs receiving pneumothorax, 87 per cent with bacteremia and only 29 per cent without bacteremia died.

(*e*) Of the dogs not receiving pneumothorax 83 per cent with bacteremia and only 20 per cent without bacteremia died.

(*f*) Of the dogs receiving pneumothorax 78 per cent of those that died and only 16 per cent of those that recovered had bacteremia.

(*g*) Of the dogs not receiving pneumothorax 83 per cent of those that died and only 20 per cent of those that recovered had bacteremia

CLINICAL EFFECTS OF PNEUMOTHORAX

The production of bilateral pneumothorax, as shown by roentgenograms, was the rule, the flimsy mediastinum of the dog allowing diffusion of gases to the healthy side. The air is especially evident above the diaphragm on the healthy side (figs. 1*A* and *B* and 2*A* and *B*). In contrast to the results for the animals with a permeable mediastinum are those for dogs for which roentgenograms of the chest are shown in figures 3 and 4. These plates demonstrate that by the production of a thickened mediastinal pleura the mediastinum of the dog may be made impermeable to gases and (as in these two cases) to fluids. This result was brought about by enclosing the lower lobe of the right lung in a

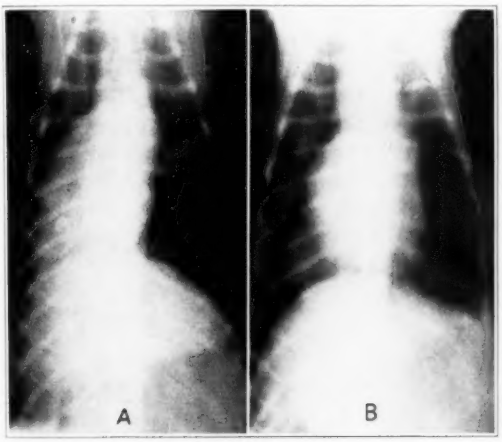

Fig. 2 (dog 61).—Roentgenograms of the lungs, showing (*A*) pneumonia of twenty-four hours' duration in the lower lobe of the right lung, with marked dextrocardia and elevation of the right side of the diaphragm, and (*B*) the appearance after the production of pneumothorax on the right side with 275 cc. of air. Dextrocardia is now absent.

rubber balloon, a procedure which results in subacute pleurisy with effusion limited to the right side.

In table 1 the usual failure to obtain relief after treatment with pneumothorax is indicated. In fact, the animals suffered general distress and dyspnea; certainly, we observed no clinical "crisis" after the production of pneumothorax, such as that reported[2] to occur experi-

2. Lieberman, L. M., and Leopold, S. S.: Therapeutic Pneumothorax in Experimental Lobar Pneumonia in Dogs, Am. J. M. Sc. **187**:315, 1934.

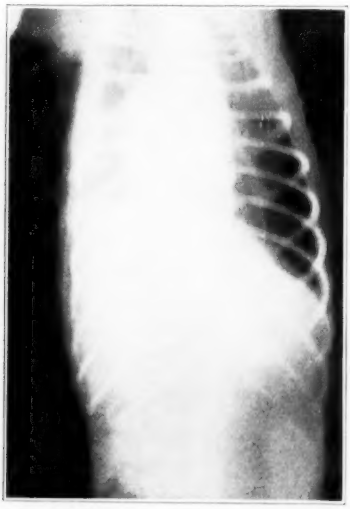

Fig. 3 (dog 22).—Roentgenogram demonstrating that the mediastinum of the dog may be made impermeable to gases and fluids by the production of subacute pleurisy with effusion. The effusion is limited to the right side by a thickened mediastinal pleura.

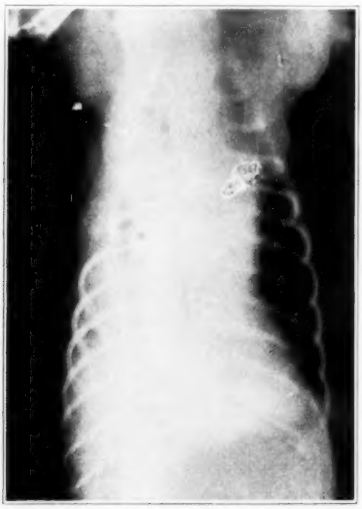

Fig. 4 (dog 31).—Roentgenogram illustrating the same result as that shown in figure 3.

mentally within from two to three days after the institution of pneumothorax. From the standpoint of the appearance, the presence of fever and the respiratory rate, nine, or 60 per cent, of fifteen toxic animals receiving pneumothorax were worse or unimproved by the third day after the insufflation of the culture, that is, after the second treatment with pneumothorax. Of equally toxic animals not receiving pneumothorax, eight, or 73 per cent, were definitely improved by the third day. Two animals (dogs 42 and 47) showing slight toxicity were worse after treatment with pneumothorax, and one of these animals died on the ninth day.

COMMENT

We shall not refer extensively to the literature on the use of pneumothorax in lobar pneumonia. The paper on the experimental work of Lieberman and Leopold [2] and the clinical report of Behrend and Cowper [3] contain a complete bibliography on the history of this subject.

Lieberman and Leopold [2] induced lobar pneumonia in dogs by modification of a method which we first devised,[4] that is, by the injection of a suspension of sedimented pneumococci into the lung with the aid of bronchoscopic observation. For anesthesia they used morphine (6 mg. per kilogram of body weight) subcutaneously and sodium amytal (15 mg. per kilogram) intraperitoneally. We have not found starch broth necessary for the production of pneumonia. What is more, in the present experiment we used much larger doses than are necessary to induce pneumonia, i. e., at least 20 cc. of broth culture (0.05 cc. of sedimented organisms) for a dog weighing 10 Kg. This was done to obtain a series of animals comparable to that of Lieberman and Leopold. In a study on elasticity of the lung, shortly to be published, we regularly produced pneumonia by the insufflation of only 0.5 to 1 cc. of a broth culture of pneumococcus, i. e., with only one twentieth to one fortieth of the doses used in the present study.

The reader will recall the significant parallelism between pneumococcic bacteremia and the mortality, regardless of whether pneumothorax was used. That pneumothorax was of little or no therapeutic value in our experiments appears to be definite, but the close correlation between bacteremia and mortality is significant. We believe that this correlation exists in the data of Lieberman and Leopold and that in their experiments as well as in ours recovery had much more relation to the absence of

3. Behrend, A., and Cowper, R. B. G.: Artificial Pneumothorax in the Treatment of Lobar Pneumonia, J. A. M. A. **102**:1907 (June 9) 1934.

4. Coryllos, P. N., and Birnbaum, G. L.: Lobar Pneumonia Considered as a Pneumococcic Massive Atelectasis of the Lung, Bull. New York Acad. Med. **4**:384 (March) 1928; footnote 1.

bacteremia than to the employment of pneumothorax (tables 2 to 5). For example, in table 2 of their paper [2] (page 320) it is shown that of fifteen dogs given pneumothorax that recovered, six, or 40 per cent, had bacteremia. On the other hand, in table 4 (page 328) it is pointed out that of the thirteen dogs not receiving pneumothorax that died, nine, or over 69 per cent, had bacteremia. Of the five dogs in their series not receiving pneumothorax that lived (table 5, page 329) only one, or 20 per cent, had bacteremia. For the dogs treated with pneumothorax that died, blood cultures were negative in all three instances, but it would have been of interest to know whether the blood from the heart contained pneumococci at death.

We take objection to the inclusion in table 4 (page 328) in the paper of Lieberman and Leopold,[2] of the data on three untreated dogs dying in twenty-four, thirty-six and thirty-six hours after insufflation of culture into the lung. These dogs are obviously not comparable subjects to be used as controls for animals receiving pneumothorax, since pneumothorax was usually given at least forty-eight hours after insufflation of Pneumococcus. It is clear that the group of animals receiving pneumothorax were able to withstand the disease for at least forty-eight hours before pneumothorax was produced. Obviously, we must begin the experiment with dogs in a comparable stage, leaving several animals to be used as controls and starting treatment of others with pneumothorax, if the merit of pneumothorax as a therapeutic measure is to be determined.

The same authors found that the animals with positive blood cultures before the production of pneumothorax usually had negative blood cultures on the day after treatment with pneumothorax. Is it not possible that the disappearance of bacteremia can occur without the employment of pneumothorax? At any rate, it is difficult to see how pneumothorax could so further collapse or immobilize a consolidated lobe as to close the blood and lymph vessels and prevent or diminish bacteremia. On the contrary, it is not difficult to see why pneumothorax can be a dangerous method by facilitating immobilization, impairing drainage and favoring bronchial obstruction in the diseased and in the uninvolved lobes.

Concerning the rôle of bacteremia in the fatal outcome of pneumonia, we have repeatedly pointed out the dual problem that exists—local pulmonary infection with production of toxins and generalized infection or bacteremia. Therapeusis must aim at both infections. In the experimental data it was evident that the incidence of mortality was high in cases of bacteremia, whether pneumothorax was used or not. In line with this reasoning is the work of Cecil and his collabo-

tors and that of other authors,[5] who showed that the mortality rate was significantly reduced by serum therapy, especially in the cases of bacteremia.

It would, of course, be difficult to state whether the bacteremia is the main factor in the mortality rate, or whether it indicates that toxins produced in the lungs are escaping through the blood and lymph capillaries of the lungs and are finding their way into the blood stream with a facility equal to that of the pneumococci. Perhaps both factors are at play. It is possible that a focus of sepsis arising from pneumococci other than the infection in the lung could account for the death after a considerable time of animals in which the lungs are normal with or without a positive culture of the blood from the heart. The fact remains that animals with bacteremia showed a much greater mortality than those without, regardless of whether pneumothorax was given. It is also noteworthy that serum therapy in cases of pneumonia in man has significantly reduced the mortality rate only in the cases of bacteremia.

Reference will now be made to one of the latest clinical investigations of pneumothorax therapy in pneumonia, the study of Behrend and Cowper.[3] There are many points in the section of their paper entitled "Theoretical Aspects" which are worthy of comment. We agree with them that "all deaths from lobar pneumonia are due directly or indirectly

5. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia: A Clinical and Bacteriologic Study of Two Thousand Typed Cases, Arch. Int. Med. **40**:253 (Sept.) 1932. Trask, J. D.; O'Donovan, C., Jr.; Moore, D. M., and Beebe, A. R.: Studies on Pneumonia in Children: I. Mortality, Blood Cultures and Humoral Antibodies in Pneumococcus Pneumonia, J. Clin. Investigation **8**:623 (June) 1930. Etinger, G. G.; Masel, I., and Wiktorow, L.: Zur Klinik und Epidemiologie der croupösen Pneumonie: I. Klinischer Verlauf und Pneumokokkentypen, Deutsches Arch. f. klin. Med. **174**:602, 1933. Cole, Rufus: Serum Treatment in Type I Lobar Pneumonia, J. A. M. A. **93**:741 (Sept. 7) 1929. Cecil, R. L., and Plummer, Norman: Pneumococcus Type I Pneumonia: A Study of 1,161 Cases, with Especial Reference to Serum Therapy, ibid. **95**:1547 (Nov. 22) 1930. Quincke, H.: Klinische Erfahrungen bei der Serumbehandlung der Pneumonie, Ergebn. d. inn. Med. u. Kinderh. **44**:655, 1932. Bullowa, J. G. M.: Studies on the Serum Treatment of Pneumonia, New York State J. Med. **33**:13 (Jan.) 1933. Sutliff, W. D., and Finland, Maxwell: Type I Pneumococcic Infections with Especial Reference to Serum Treatment, New England J. Med. **210**:237 (Feb. 1) 1934. Kereszturi, C., and Hauptman, D.: The Serum Treatment of Pneumonia in Children, J. Pediat. **4**:331 (March) 1934. Avery, O. T.; Chickering, H. T.; Cole, Rufus, and Dochez, A. R.: Acute Lobar Pneumonia: Prevention and Serum Treatment, Monograph 7, Rockefeller Institute for Medical Research, 1917. Gundel, B.: Die Bakteriologie, Epidemiologie und spezifische Therapie der Pneumokokkeninfektionen des Menschen unter besonderer Berücksichtigung der Pneumonie, Ergebn. d. Hyg., Bakt., Immunitätsforsch. u. exper. Therap. **12**:131, 1931.

to toxemia." On other points we disagree, such as, for example, the following (page 1907):

> When acute inflammation occurs in a part of the body that is functionally or anatomically movable, experience has taught that the primary treatment of the affected part is rest. We may cite, for example, the splinting of the joint in acute arthritides, the immobilization of the extremities in cellulitis and the strapping of the chest in pleurisy. The object is to supplement by mechanical means the rational demands of the organism for rest.
>
> Lobar pneumonia furnishes an excellent example of acute inflammation in an organ whose function requires almost constant movement. Attempts of the body to limit motion of the lung by decreased expansion and shallow frequent respirations cannot be too successful. The introduction of air into the pleural cavity by artificial pneumothorax furnishes a mechanical aid that admirably accomplishes the desired results.
>
> . . . When acutely inflamed pleural surfaces are separated, the pain formerly caused by every respiratory excursion disappears.

We have repeatedly emphasized the part played by stagnation of secretion or exudate in the bronchi, bronchial obstruction and absorption of air in the pathogenesis of lobar pneumonia.[6] As the affected lobe shrinks and exudate accumulates, reaeration or expulsion of secretions by respiration and cough becomes increasingly difficult, if not impossible. For this reason, even temporary accumulations of secretion and exudate in or obstructing the bronchus of a lobe may initiate pneumonic consolidation of the lobe, which may not begin to clear before seven, eight or nine days, when liquefaction of the fibrinous exudate allows gradual ingress of air into and reaeration of the lobe ("crisis"). The comparison with acutely infected joints is not well taken, because experience in the World War has definitely proved that a septic joint needs drainage and not immobilization. In tuberculous joints immobilization acts by decreasing the degree of hematosis and oxygenation of tissues, which is a different mechanism. Therefore, rest of a lobe harboring pyogenic organisms and secretions is the last thing to be desired if bronchial obstruction, atelectasis and pneumonitis are to be avoided. In the pathogenesis of pneumonia, bronchial obstruction, absorption of air, shrinkage of the lung and exudation go hand in hand. We have shown[1] that in vitro pneumococci grow more profusely with a partial reduction of oxygen and that in vivo relatively small doses of pneumococci introduced below a mechanical obstruction of the bronchi produced very toxic pneumonia.

It is not difficult to visualize the mechanism by which pneumothorax could relieve pleural pain by separation of the visceral pleura of a con-

6. Coryllos, P. N., and Birnbaum, G. L.: Bronchial Obstruction: Its Relation to Atelectasis, Bronchopneumonia and Lobar Pneumonia; a Roentgenographic Experimental and Clinical Study, Am. J. Roentgenol. **22**:401, 1929.

solidated lobe from the parietal. It is also possible that pneumothorax may, as occasionally it does in rare cases of bronchiectasis, facilitate drainage of the bronchi; however, it is reasonable to believe that the reverse occurs.

Behrend and Cowper [8] pointed to numerous reports of studies in the literature showing that pneumothorax causes a decreased circulation of blood and lymph in the capillaries of the lung. We agree with these views, our own work showing a decreased circulation of blood in the atelectatic or pneumonic lung. We agree that "lymph stasis with diminution of absorption of toxins has long been held largely responsible for the beneficent effect of artificial pneumothorax in pulmonary tuberculosis by Riviere, Warnecke, Mariotte, Gardner and others." We disagree with the statement: "It doubtless functions in a similar manner in lobar pneumonia."

The statement that pneumothorax functions in a similar manner in lobar pneumonia and in tuberculosis is not warranted. In pneumonia pneumothorax is theoretically a threefold evil: It may collapse healthy tissue of the lung and thus hinder respiration; it may facilitate bronchial obstruction and thus induce pneumonia in a healthy or a partially affected lung, and it may hinder reexpansion of the pneumonic lung.

Is one to be forced to believe that a consolidated pneumonic lobe can be collapsed by the use of pneumothorax? Theoretically, however, a lobe with an early stage of pneumonia which is partially collapsed and the capillaries of which are still patent could be affected by pneumothorax through a diminished flow of blood and lymph, but pneumothorax, by hindering reaeration and facilitating stagnation of exudates and obstruction of the bronchi, would tend to further the pneumonic process. Therefore, again, is one to believe that in an early stage of lobar pneumonia collapse therapy is rational and that attempts to improve the respiration of a lobe by hyperventilation, drainage by means of bronchoscopy [7] or any other method are irrational? Patency of the bronchi and alveolar ventilation are the best defense of the lung against infection, which it resists in spite of the presence of numerous organisms in the bronchial tree.

The process of recovery in lobar pneumonia, we believe, starts when the fibrinous exudate becomes sufficiently liquid, through the action of proteolytic ferments of the white cells, to allow ingress of air and reaeration of the lung. Likewise, we believe that in the early stage of lobar pneumonia, before "fixation" of the alveoli by fibrinous exudate, every means should be utilized to encourage respiration of the lobe and to pre-

7. Coryllos, P. N.: Bronchoscopic Findings in Lobar Pneumonia, Am. J. M. Sc. **178**:8, 1929.

vent or relieve obstruction of the bronchi, with the possible evil train of pathologic changes. For these reasons, we are opposed to the use of pneumothorax in lobar pneumonia, in either the early or the late stage. On the contrary, we are heartily in favor of collapse therapy with pneumothorax in tuberculosis, for in this condition compression, rest and atelectasis of a lobe are detrimental to the growth of the tubercle bacillus, which is strictly an aerobe. The mechanism of cure and therapy in tuberculosis, as pointed out by one of us (P. N. C.),[8] is thus very different from that in lobar pneumonia. The rational therapy in lobar pneumonia and in pulmonary tuberculosis are diametrically opposed.

Behrend and Cowper reported the clinical relief of pain, toxicity, fever and cyanosis by the use of pneumothorax. They stated[3] (page 1,908) that with pneumothorax therapy the "cough is diminished and the amount of sputum becomes almost negligible." Diminution of cough and expectoration, we believe, is a distinct danger through facilitating bronchial obstruction in healthy lobes and hindering the reaeration of a pneumonic lobe. We agree with their statement that the spread of the pneumococcic process to the opposite side "may constitute a real danger in the use of this form of therapy." Lastly, it is of interest that in the eleven cases which these authors reported, the only two patients who died had had a positive blood culture, again a corroboration of the conclusion based on our experimental work that there is a close connection between bacteremia and mortality in lobar pneumonia.

In a protean disease like pneumonia it is dangerous to arrive at hasty conclusions based on a limited number of cases. The consensus as to the real usefulness of serum treatment even in pneumonia due to type I Pneumococcus is far from unanimous, notwithstanding the extensive statistics now available in the literature. A careful and impartial analysis of these statistics shows that the mortality in cases of pneumonia uncomplicated by bacteremia has been influenced little if any by the use of serum and that in cases with bacteremia, in which serum is more efficient, the mortality when treatment is given still varies widely in different years and in different localities. It is our opinion that serum injected into the circulating blood may influence bacteremia but that it is without marked action on the pulmonary focus, because little blood circulates in the consolidated and atelectatic pneumonic lung.

The pathogenesis and pathologic physiology and bacteriology of lobar pneumonia point to the rapid liberation and drainage of the obstructed bronchi and the reaeration of the lung as the only logical treatment. The results obtained by one of us (P. N. C.) with drainage by means of

8. Coryllos, P. N.: Wie führen Ruhe- und Kollapsbehandlung zur Heilung der Lungentuberkulose? Deutsche Ztschr. f. Chir. **243**:701, 1934; Ueber die Bedeutung der Atelektase für den Verlauf der Lungentuberkulose, Beitr. z. Klin. d. Tuberk. **85**:339, 1934.

bronchoscopy in cases of severe lobar pneumonia is in favor of this conception.

In support of our opinion we shall briefly report here an instance of "miraculous success" obtained by pneumothorax in a patient with severe lobar pneumonia, referred by Dr. Malavazos, of Newark, to one of us (P. N. C.).

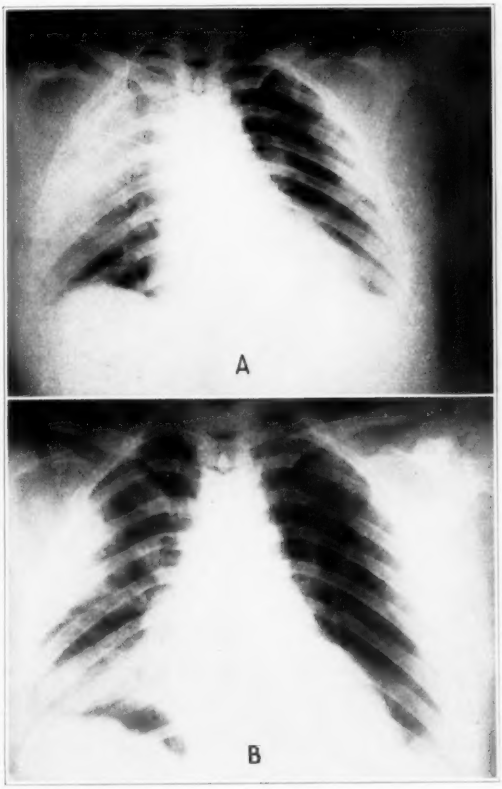

Fig. 5.—Roentgenograms of the chest of C. P., showing (*A*) pneumonia of the upper and middle lobes of the right lung and (*B*) the appearance forty-eight hours after the production of pneumothorax on the right side with 150 cc. of air.

REPORT OF CASE

C. P., a white woman aged 32, had an onset of pneumonia on May 3, 1934, with prolonged chill and pain in the right side of the chest. The physical examination on May 6 revealed a temperature of 104 F., a pulse rate of 135 and consolidation of the upper lobe of the right lung. On that day she was admitted to the Beth Israel Hospital, in Newark, N. J. The blood examination on May 7

showed: white cells 18,500, polymorphonuclears 60 per cent, stab forms from 2 to 4 per cent and lymphocytes 13 per cent. On May 8 the blood culture was positive for Pneumococcus type V. Twenty thousand units of polyvalent serum was administered in the course of twenty-four hours (on May 8). The temperature decreased from 105 to 101 F., and diaphoresis was profuse. However, a few hours later the temperature increased to 105.6 F., and examination showed extension of consolidation to the middle and upper lobes of the right lung, as shown in the roentgenogram (fig. 5 *A*). During the next three days (from May 9 to May 12) the temperature remained between 104 and 106 F., reaching the highest

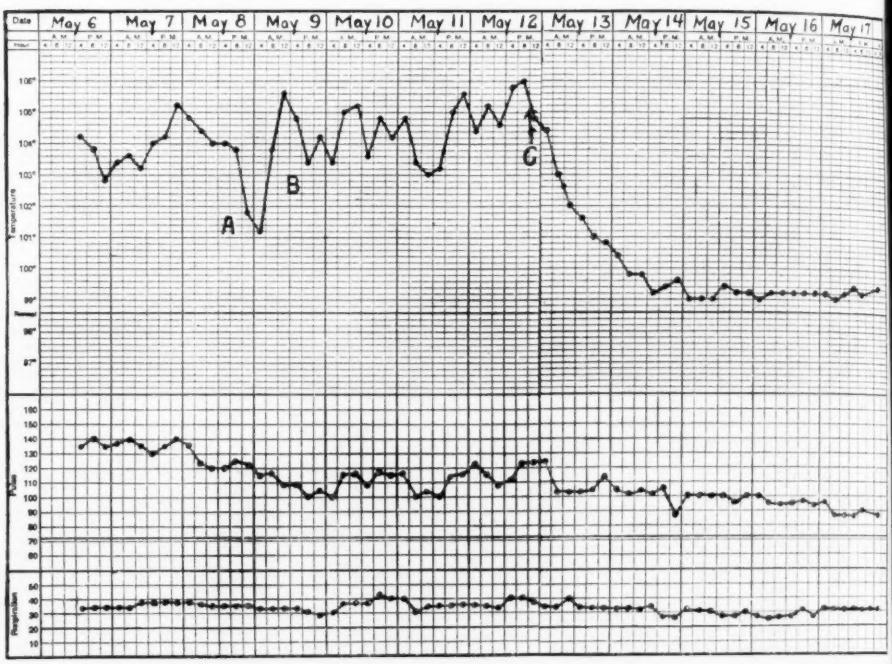

Fig. 6.—Clinical chart for the patient, roentgenograms of whose chest are shown in figure 5, indicating (*A*) the crisis of the initial process, (*B*) the beginning of the secondary process and (*C*) the point at which artificial pneumothorax was produced.

point at 8 p. m., May 12. At 11 p. m. of that day artificial pneumothorax was produced by one of us (P. N. C.), 150 cc. of air being injected into the right pleural cavity.

Are we to attribute this success to pneumothorax? We do not believe that we should. In this case the course of recovery was strikingly similar to that in postoperative atelectasis, namely, productive cough, profuse expectoration and rapid decrease in temperature by crisis. In

other words, liberation of the obstructed bronchi and drainage of the pulmonary foci are effected as is drainage in cases of abscess of the lung or of any other organ or part of the body. The introduction of 150 cc. of air cannot reasonably produce such an effect and with such lightning speed. The only reasonable explanation of the success of the use of pneumothorax in this case is that it was applied at the opportune moment when the crisis was about to occur.

From consideration of the experimental and clinical data we believe that we can conclude that pneumothorax has no real therapeutic effect in pneumonia.

SUMMARY AND CONCLUSIONS

In a group of forty dogs with experimentally induced lobar pneumonia the effects of artificial pneumothorax as a therapeutic measure were studied. Various analyses of the data were also made from the standpoint of the incidence of toxicity, bacteremia and mortality.

It was found that the mortality rate closely paralleled the incidence of bacteremia, regardless of whether pneumothorax was used. Pneumothorax was found ineffective for the relief of clinical symptoms or for reduction of the mortality rate.

The theoretical disadvantages of pneumothorax were pointed out. The dual infectious nature of the disease was emphasized, namely, the local pulmonary infection and the generalized bacteremia. Caution was urged in the evaluation of the clinical merit of pneumothorax in lobar pneumonia.

The facts in a case of lobar pneumonia in man, occurring in our personal experience, in which pneumothorax was followed by crisis within twenty-four hours were analyzed, and the relation of pneumothorax to this "miraculous cure" was discussed.

It is our opinion that artificial pneumothorax may relieve pleuritic pain but that it does not influence the crisis in lobar pneumonia.

Progress in Internal Medicine

BRIGHT'S DISEASE: A REVIEW OF RECENT LITERATURE

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As in the previous review written one year ago, I make no attempt to include all of the numerous articles which have appeared in this field but merely review some of those which most clearly indicate the present trend of thought and those which mark new advances in the frontier of knowledge.

GLOMERULONEPHRITIS

Concerning the etiology of diffuse glomerulonephritis, some of the most important work of the last decade is that of Longcope and his associates, an initial report of which appeared in 1927.[1] The sequel to this work has recently been reported by Winkenwerder, MacLeod and Baker,[2] who have made an analysis of the associated infections in 78 cases of hemorrhagic nephritis, 40 of which were included in the original report of Longcope in 1927. Thus it becomes possible now to give a better evaluation of the work of the Longcope school than would have been the case a year ago.

Winkenwerder, McLeod and Baker[2] present even stronger evidence than was given in the first report of the close relationship between infection with Streptococcus haemolyticus and glomerular nephritis. Infection of the upper respiratory tract with the beta type of this organism precedes the nephritis in the great majority of cases. The alpha type is apparently responsible for a small number of cases. When the onset of nephritis is preceded by acute infection, there is apparent a greater tendency to healing or to latency as a sequel than when the onset is preceded by a chronic infection, which seems to favor persistence of the infection and a chronic progressive type of nephritis. In 10 or 12 per cent of the cases no connection with streptococcic

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1. Longcope, W. T.; O'Brien, D. P.; McGuire, J.; Hansen, O. C., and Denny, E. R.: Relationship of Acute Infections to Glomerular Nephritis, J.Clin.Investigation **5**:7, 1927.

2. Winkenwerder, W. L.: McLeod, N., and Baker, M.: Infection and Hemorrhagic Nephritis, Arch. Int. Med. **56**:297 (Aug.) 1935.

infection was proved. There was no evidence that pneumococcic pneumonia, rheumatic fever or syphilis had any causal relationship to the nephritis.

Seasonal variations in the frequency of hemorrhagic nephritis corresponded with those of respiratory infection in Baltimore. The prodromal period between the onset of infection and the appearance of nephritis was from three to twenty-eight days, most frequently seven days, with an average length of ten and nine-tenths days. This period is somewhat shorter than previous reports would indicate.

Exacerbations of nephritis are usually due to streptococcic infection of the respiratory tract and are commonest in the latent and progressive forms of nephritis, though exacerbation may be induced by surgical procedure. The prodromal period between infection and exacerbation is short, from twenty-four to forty-eight hours. When streptococcic infection occurred during convalescence from nephritis it did not prevent recovery; and after recovery was established it rarely caused a relapse. Most characteristic of the progressive types of nephritis was a "carrier state" without recurring evidences of active infection. The character of the causal infection seems to determine the outcome of hemorrhagic nephritis. Acute reactions to infection predispose to recovery. Chronic infection in which the resistive reactions are incomplete and the organisms persist result in a chronic progressive nephritis.

Attempts to produce a chronic progressive diffuse hemorrhagic nephritis have almost universally failed, no doubt because chronic streptococcic infections are difficult to establish in animals. In 1931 Lukens and Longcope [3] were able to produce acute diffuse glomerulitis, and by a variety of methods other workers have been able to effect somewhat similar results. One of the most recent attempts is that of Vallery-Radot, Dérot and Gauthier-Villars,[4] who produced glomerular lesions by the injection into rabbits of filtrates of cultures of virulent streptococci. There developed serous effusions, azotemia and albuminuria. No mention is made of the occurrence of hematuria in these animals. Histologically, in addition to glomerulitis, there were a few tubular and some interstitial changes, but nothing resembling chronic glomerular nephritis was produced.

In the French literature there is recurring reference to the problem of the "war nephritis." Célice and Albeaux-Fernet [5] report a case of

3. Lukens, F. D. W., and Longcope, W. T.: Experimental Acute Glomerulitis, J. Exper. Med. **53**:511, 1931.

4. Vallery-Radot, P.; Dérot, M., and Gauthier-Villars, P.: Néphrites expérimentales obtenues par l'injection au lapin de filtrats streptococciques, Ann. de méd. **38**:100 (June) 1935.

5. Célice, J., and Albeaux-Fernet, M.: Forme rénale pure de spirochétose, Ann. de méd. **38**:70, 1935.

infection with a spirochete, without jaundice, but characterized by acute nephritis of a type commonly observed during the World War. In 11 of Winkenwerder's [2] series of 78 cases of hemorrhagic nephritis no relation to streptococcic infection could be discovered. One wonders what proportion of the cases without streptococcic infection may be of spirochetal origin.

Seegal, Seegal and Lyttle [6] have analyzed the data concerning the infections preceding acute hemorrhagic nephritis in the histories of 379 cases. The results agree with those of the Longcope-Winkenwerder series quite well. In the majority of cases the preceding infection was a deep streptococcic infection, such as cervical lymphadenitis, peritonsillar abscess, otitis media or mastoiditis. Scarlet fever played a relatively minor rôle. In a small percentage of cases the nephritis was preceded by pneumococcic pneumonia or an infection with Staphylococcus, and in a few cases it was preceded by a fever of unknown origin. Other points of interest in their observations were the facts that 50 per cent of the cases occurred in persons under the age of 10 years and 70 per cent in persons under 20 and that the incidence in males predominated over that in females in a ratio of 2:1.

In another paper Seegal, Seegal and Jost [7] compared the incidence of scarlet fever, acute rheumatic fever and acute nephritis at different latitudes in the United States. Scarlet fever and rheumatic fever are apparently much more prevalent in the northern latitudes, while the incidence of acute nephritis is nearly as high in southern as in northern latitudes.

A new contribution to the pathologic histology of glomerulonephritis has been made by MacCallum,[8] who reviewed the glomerular changes observed in the last 5,000 autopsies at the Johns Hopkins Hospital by means of a special staining technic. He noted that the capillaries of the glomerulus stand in the same relation to the epithelium of the glomerulus as the capillaries of the tubules do to the epithelium of the tubules. This suggests to MacCallum that the epithelium must govern the functions of the glomerulus. He observed that the basement membrane is separated from the wall of the capillaries and that connective tissue between the capillaries is to be found in the glomerular tufts. Various injuries result in reparative processes which produce much new con-

6. Seegal, D.; Seegal, B. C., and Lyttle, J. D.: The Nature of the Preceding Infection in Acute Glomerulonephritis in Two New York Hospitals and in Four Southern Hospitals, J. A. M. A. **105**:17 (July 6) 1935.

7. Seegal, D.; Seegal, B. C., and Jost, E. L.: Geographic Distribution of Rheumatic Fever, Scarlet Fever and Acute Glomerulonephritis in North America, Am. J. M. Sc. **190**:383 (Sept.) 1935.

8. MacCallum, W. G.: Glomerular Changes in Nephritis, Bull. Johns Hopkins Hosp. **55**:416, 1934.

nective tissue between the capillaries, displacing and compressing them. In some instances this may be associated with a great proliferation of epithelium. MacCallum could find no case in which endothelial proliferation led to the obstruction of capillaries, so that he prefers to speak of "intercapillary" rather than "intracapillary" glomerulonephritis. When amyloid occurred it was found between the basement membrane and the capillary.

Another interesting morphologic study is that of Oliver and Luey,[9] who have discovered aglomerular tubules in contracted kidneys of certain persons with glomerulonephritis. In some instances a tubule may survive the complete occlusion of its glomerulus, owing to the continued patency of the vessel of Ludwig, which makes a direct communication between the afferent arteriole and the capillaries of the tubules. Oliver and Luey speculate somewhat on the possibilities of function in these surviving tubules on the basis of analogies in fish with aglomerular nephrons.

DEGENERATIVE FORMS OF BRIGHT'S DISEASE

In the previous review of this subject attention was drawn to the growing tendency to cast doubt on the existence of a true pure lipoid nephrosis as distinct from the nephrotic type of chronic glomerulonephritis. In the past year this tendency has received further impetus. Vallery-Radot, Delafontaine and Trombert [10] report some cases which were supposed to have been examples of true lipoid nephrosis in which the condition subsequently became uremic. These authors believe that this occurrence is not infrequent if the cases of so-called nephrosis are followed for a sufficiently long time.

Blackman [11] reports on the anatomic findings in cases of the classic syndrome of lipoid nephrosis which proved at autopsy to be instances of diffuse glomerulonephritis. The same author studied the forms of nephritis which were produced experimentally by means of a pneumococcus toxin.[12] He observed that the quantity of toxin given and the degree of immunity which develops are the important factors in determining the histologic lesions produced in the kidneys as well as the

9. Oliver, J., and Luey, A. S.: Plastic Studies in Abnormal Renal Architecture: III. The Aglomerular Nephrons of Terminal Hemorrhagic Bright's Disease, Arch. Path. **19**:1 (Jan.) 1935.

10. Vallery-Radot, P.; Delafontaine, P., and Trombert, J.: L'évolution de la "nephrose lipoidique" vers l'azotémie, Ann. de méd. **38**:79 (June) 1935.

11. Blackman, S. S.: Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis: I. Clinical and Anatomical Studies, Bull. Johns Hopkins Hosp. **55**:1, 1934.

12. Blackman, S. S.: Pneumococcal Lipoid Nephrosis and the Relation Between Nephrosis and Nephritis: II. Experimental Studies, Bull. Johns Hopkins Hosp. **55**:85, 1934.

clinical manifestations of these forms. From his work it would appear that predominance of degenerative change is noted when immunity to the toxin is low and that the features of progressive glomerulonephritis begin to appear as the immunity increases. Blackman's conception of the process of glomerulitis seems to follow that of MacCallum.[8] When immunity is high the process of healing takes place, and this is characterized by intercapillary fibrosis resulting in progressive obliteration and excessive regeneration of epithelium. He finds the chief anatomic distinction between nephrosis and glomerulonephritis to be the absence of coagula containing fibrin within the glomeruli in the former. In the absence of these, organization and formation of scar tissue do not occur.

Blackman's views on the pathogenesis of lipoid nephrosis and glomerulonephrosis [13] are stimulating and important. The papers may be criticized for a style suggestively polemic, so that their objectivity is slightly marred by the impression of special pleading.

The occasional association of renal degeneration with the excretion of Bence-Jones protein is well known. Forbus, Perlzweig, Parfentjev and Burwell [14] have investigated the problem experimentally. In a case in man the excretion of large amounts of this protein led to its precipitation in the tubules, with the formation of peculiar casts. When these completely obstructed a tubule a foreign body reaction resulted in extensive secondary changes in the nephron, leading to its destruction and fibrous replacement. Although the kidneys of certain animals are permeable to Bence-Jones' protein, its administration in large amounts over a period of days did not produce injury detectable by the microscope. In one dog a few isolated lesions resembling those in man were produced. Failure to reproduce the picture presented by the human patient may have been due to insufficient time or to the absence of the special conditions which led to the precipitation of the protein in the tubules.

The question of an optimal diet for promoting the gain of nitrogen in cases of nephrosis is discussed by Liu and Chu.[15] The authors report observations on 2 patients with the nephrotic syndrome. One of the patients had microscopic hematuria (presumably glomerulonephritis), and the other had syphilis but did not have demonstrable hematuria. Optimal gains of nitrogen occurred when the dietary protein furnished from 12 to 13 per cent of the total number of calories. The authors

13. Blackman, S. S.: On the Pathogenesis of Lipoid Nephrosis and Progressive Glomerulonephritis, Bull. Johns Hopkins Hosp. **57**:70, 1935.

14. Forbus, W. D.; Perlzweig, W. A.; Parfentjev, I. A., and Burwell, J. C.: Bence-Jones Protein Excretion and Its Effects upon the Kidney, Bull. Johns Hopkins Hosp. **57**:47, 1935.

15. Liu, Shih-Hao, and Chu, Hsien-I: An Optimal Diet in Promoting Nitrogen Gain in Nephrosis, J. Clin. Investigation **14**:293 (May) 1935.

found that the positive nitrogen balance was not increased when a higher proportion of protein was given. In spite of the large amount of nitrogen gained the protein content of the plasma was relatively little affected. In the patient with hematuria the amount of plasma protein remained low and albuminuria continued unabated. In the patient without hematuria the albuminuria gradually diminished and the concentration of protein in the plasma increased.

Similar studies were made by Keutmann and Bassett,[16] who studied 3 patients in the nephrotic stage of glomerulonephritis. Two of these patients failed to show an increase in the amount of circulating protein in spite of an enormous deposition of nitrogen in their bodies. The third patient slowly improved.

The observations of Keutmann and Bassett [16] show that there is no lack of ability in the nephrotic person to synthesize new protein. The amount synthesized was calculated as the sum of protein stored and protein in the urine. By a comparison of observations made during periods with the patient on a basic diet with those made in alternating periods during which specific supplements were added, an attempt was made to determine the degree of utilization of the supplements, which consisted of egg white, lactalbumin and protein of liver residue. When the intake of protein was increased the amount of protein in the urine usually increased, an effect which the authors attribute to an increased perfusion of the kidneys.

From the results reported in these two papers by Keutmann and Bassett it is clear that the nephrotic state does not involve a failure of regenerative synthesis of protein. It is also clear that an increase in the amount of circulating proteins of the plasma can be effected only through the mechanisms which increase the ability of the capillary membranes to retain them, that is, through a decrease in permeability.

Yanagi [17] has made some interesting observations on the stability of the protein in the plasma as indicated by the length of time during which the maximum pressure which is developed in an osmometer is maintained. The maximum pressure developed by a normal amount of protein in the serum is maintained from sixteen to eighteen hours. In serums with a low concentration of protein the pressure rose to a maximum in from three to five hours, after which a gradual decrease occurred. This reduced stability could be reproduced experimentally by dilution of normal serum with physiologic solution of sodium

16. Keutmann, E. H., and Bassett, S. H.: Dietary Protein in Hemorrhagic Bright's Disease: II. The Effect of Diet on Serum Proteins, Proteinuria and Tissue Protein, J.Clin.Investigation **14**:871 (Nov.) 1935.

17. Yanagi, K.: A Clinical and Experimental Study of the Colloid Osmotic Pressure of Serum Protein, J. Clin. Investigation **14**:853 (Nov.) 1935.

chloride or with an ultrafiltrate from normal serum. If serum with a low concentration of protein was concentrated to 6 per cent by ultrafiltration the curve of the osmotic pressure resembled that of normal serum.

For a number of years Grabfield and his co-workers have been concerned with the nature of "deposit protein." The problem has been approached by a study of the differences in the excretion of nitrogen and of sulfur produced by the exhibition of iodides and salicylates in normal and nephritic subjects. A tendency for the edematous subject to retain sulfur in excess of nitrogen has been noted. Grabfield and Adams [18] reported experiments in which diets low in sulfur were given to 7 patients, 3 of whom had a normal concentration of protein in the serum and 4 of whom had a low concentration. On such diets the nephrotic patients excreted less sulfur than did those whose concentration of protein was normal. The authors wisely refrain from trying to explain the phenomenon at this time. However, the accumulating data may ultimately throw some light on the nature of "deposit protein."

In the treatment of edema in persons with nephrosis attempts have been made to increase the colloid osmotic pressure of the blood plasma by the injection of solutions of acacia. Dick, Warweg and Andersch [19] report experiences with this procedure which indicate that it is not only futile but harmful. Acacia was subsequently found in edema fluids and in appreciable amounts in the liver and other organs and tissues. It was noted that these changes were accompanied by a further decrease in the protein content of the serum. In view of such experience the further use of acacia seems to be unwarranted.

NEPHRITIS AND THE TOXEMIAS OF PREGNANCY

Herrick and Tillman [20] contribute a valuable study in recording the results of a prolonged period of observation of 594 women with toxemia of pregnancy. The observations, which ranged in duration from one to twenty-two years, with an average of five and six-tenths years, revealed the startling fact that more than one half of the survivors of the condition were found to have symptoms and signs of either glomerulonephritis or hypertensive cardiovascular disease within a period of three years.

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18. Grabfield, G. P., and Adams, L. G.: Nitrogen and Sulphur Metabolism in Bright's Disease: VI. Effect of Diets Low in Sulphur on the Excretion of Sulphur, Arch. Int. Med. **55**:360 (March) 1935.

19. Dick, M. W.; Warweg, E., and Andersch, M.: Acacia in the Treatment of Nephrosis, J. A. M. A. **105**:654 (Aug. 31) 1935.

20. Herrick, W. W., and Tillman, A. J. B.: Toxemia of Pregnancy: Its Relation to Cardiovascular and Renal Disease, Arch. Int. Med. **55**:643 (April) 1935.

In 11 cases an autopsy was performed; the anatomic diagnosis of chronic glomerulonephritis was made in 4 cases and that of cardiovascular disease with hypertension in 7. The clinical as well as the pathologic evidence suggests a continuous chain of events in the cases with cardiovascular sequelae in which the injury of the acute phase fails to heal and hyperpiesis becomes permanent. In women with glomerulonephritis, whether latent or manifest, pregnancy activates the disease and aggravates it roughly in proportion to the size of the fetus. In such women repeated pregnancies encroach further on the factor of safety of the kidney and should be avoided.

In making a differential diagnosis between the types of toxemia occurring during pregnancy the Addis count of the urinary sediment will probably assume increasing importance. In this connection one is indebted to Elden and Cooney [21] for a study of urinary sediments and of the urea clearance in women during the last trimester of a normal pregnancy. In 19 normal women the cast count ranged from 0 to 10,000, the erythrocyte count from 47,000 to 1,900,000 and the count for epithelial cells and leukocytes from 25,000 to 6,000,000 per twelve hour night specimen. The urea clearance varied from 60 to 118 per cent of the average normal standard clearance. Nice [22] has also studied the urea clearance during normal pregnancy, observing that the mean value ante partum was 153 per cent, that the mean value post partum was 95.5 per cent and that the mean value for nonpregnant normal women was 105 per cent of the standard clearance values of Van Slyke.

Harvey Cushing [23] reports the finding of pronounced basophilic invasion of the neurohypophysis in 6 fatal cases of eclampsia of pregnancy. There were 3 other cases in which this finding was less definite. Cushing believes that this is the histopathologic basis of eclampsia and of some types of primary hypertension of young people.

Thus it appears that the renal lesions of the toxemias of pregnancy are coming to be thought of as separate entities. Certainly Herrick and Tillman have shown that a substantial number of them belong to the realm of glomerulonephritis and the remainder to that of the vascular nephropathies. The usefulness of the term nephrosis of pregnancy is doubtful.

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21. Elden, C. A., and Cooney, J. W.: The Addis Sediment Count and Blood Urea Clearance Test in Normal Pregnant Women, J. Clin. Investigation **14**:889 (Nov.) 1935.

22. Nice, M.: Kidney Function During Normal Pregnancy: I. The Increased Urea Clearance of Normal Pregnancy, J. Clin. Investigation **14**:575 (Sept.) 1935.

23. Cushing, H.: Hyperactivation of the Neurohypophysis as the Pathological Basis of Eclampsia and Other Hypertensive States, Am. J. Path. **10**:145, 1934.

ARTERIOSCLEROTIC FORMS OF BRIGHT'S DISEASE—THE NEPHROSCLEROSES

There has been for some time a widespread appreciation of the existence of two types of essential hypertension, expressed in the German conception of the "red" and the "pale" type or in current usage benign and malignant. The conception of malignant hypertension as a nosologic entity is still somewhat confused, though much has been done to establish histologic differentiations between the arteriolar changes in the benign and those in the malignant forms and to distinguish between the glomerular changes which characterize glomerulonephritis and malignant nephrosclerosis. Benign essential hypertension can and frequently does exhibit rather fulminating phenomena in its later stages, which tend to confuse some clinicians on the "malignancy" of the disease. A recent paper by MacMahon and Pratt [24] is timely in that it gives a general review of the anatomic and clinical phenomena which justify the nosologic differentiation of a malignant type of hypertension from the more common benign type.

MacMahon, Close and Hass [25] have made a careful anatomic study of the cardiovascular and renal lesions in 2 cases of basophilic adenoma of the pituitary. The lesions found corresponded closely with the picture originally described as malignant nephrosclerosis by Fahr. A similar case is reported by Close.[26] Ahlström [27] also describes the hypophyseal changes in 2 cases of malignant nephrosclerosis. In 1 case there was a small chromophobe adenoma in an apparently normal anterior lobe, with pronounced basophilic infiltration of the neurohypophysis. In a second case there was a cyst of the pars intermedia which was filled with a basophilic colloid material. There was also some infiltration of the posterior lobe by basophil cells. As one reviews these papers, the conviction grows that malignant nephrosclerosis is a distinct nosologic entity not to be confused with benign hypertension but closely related to eclampsia of pregnancy and to basophilia of the pituitary body.

In the field of treatment of hypertension there are two new developments of great interest. Page and Heuer [28] report the surgical section

24. MacMahon, H. E., and Pratt, J. H.: Malignant Nephrosclerosis (Malignant Hypertension), Am. J. M. Sc. **189**:221 (Feb.) 1935.

25. MacMahon, H. E.; Close, H. G., and Hass, G.: Cardiovascular Renal Changes Associated with Basophil Adenoma of the Anterior Lobe of the Pituitary (Cushing's Syndrome), Am. J. Path. **10**:177, 1934.

26. Close, H. G.: Basophil Adenoma of the Pituitary Gland with Renal Changes, Brit. M. J. **1**:356 (Feb. 23) 1935.

27. Ahlström, C. G.: Hypophysial Changes in Malignant Nephrosclerosis, Acta path. et microbiol. Scandinav. **12**:232, 1935.

28. Page, I. H., and Heuer, G. J.: A Surgical Treatment of Essential Hypertension, J. Clin. Investigation **14**:22 (Jan.) 1935.

of the anterior roots of the spinal nerves from the sixth thoracic to the second lumbar vertebra in a young girl with hypertension. As a result of this procedure the blood pressure quickly returned to normal; no change in the excretion of urea was noted; there was slight loss of power of concentration and no increase in hematuria. This operation of Page and Heuer is quite formidable, requiring a laminectomy and producing paralysis of the abdominal muscles. A second procedure has been tried by Peet,[29] who has published a preliminary report of section of the roots of the splanchnic nerves in the lower thoracic segments. Since this leaves the abdominal musculature intact and since it can be more easily carried out, a complete report will be awaited with great interest.

CONTRACTED KIDNEY DUE TO PYELITIS

Longcope and Winkenwerder [30] describe the clinical features of this condition, which is probably not very rare. It is more common in women, characterized by attacks of lumbar pain and sometimes of fever. It may be symptomless up to the uremic stage. Of 9 cases studied, death occurred in 5 of uremia, in 5 there was high blood pressure and in 4 there were pathologic changes in the retina. Progressive anemia and polyuria were common features. The pyelograms revealed irregularities of the pelvis and calices. The urine in such cases is of low specific gravity and contains little albumin and few casts. Erythrocytes were present in 1 case only, in which there were ulcers in the bladder. Impaired renal function often preceded death by years and often progressed before symptoms were noted. At autopsy the kidneys were small, scarred and uneven, with a distorted irregular dilated pelvis and varying degrees of inflammation. Between scars relatively normal renal structure was preserved.

CYSTIC DISEASE OF THE KIDNEYS

Bell [31] gives the incidence of this condition as 1 in each 500 autopsies. In from 5 to 10 per cent of the cases it is unilateral. He classifies the condition in two types: surgical, in which signs are referable to one kidney (pain, tumor, hematuria, infection, etc.), and medical, in which acute or chronic renal insufficiency with hypertension and cardiovascular changes is observed. Willer [32] discusses the relationship of cystic dis-

29. Peet, M. M.: Splanchnic Section for Hypertension: Preliminary Report, Univ. Hosp. Bull., Ann Arbor **1**:17 (June) 1935.

30. Longcope, W. T., and Winkenwerder, W. L.: Clinical Features of the Contracted Kidney Due to Pyelonephritis, Bull. Johns Hopkins Hosp. **53**:255, 1933.

31. Bell, E. T.: Cystic Disease of the Kidneys, Am. J. Path. **11**:373, 1935.

32. Willer, H.: Ueber kongenitale Zystennieren und Blutdruck, München. med. Wchnschr. **82**:1437 (Sept. 6) 1935.

ease and hypertension. He believes that their concurrence is a matter of chance and that the high blood pressure is not secondary to the loss of renal tissue.

RENAL DISEASE AND THE PARATHYROID GLANDS

Albright, Baird, Cope and Bloomberg [33] collected reports of 83 cases of hyperparathyroidism, in 43 of which some type of renal damage was observed. This was attributed to the precipitation of calcium in the tubules, with resultant sclerosis, contraction and insufficiency, or to the formation of calculi in the pelvis with associated pyelonephritis.

Thirty years ago MacCallum [34] reported the finding of a tumor of a parathyroid gland in a young woman who died of glomerulonephritis. The remaining parathyroid glands were normal. Two other cases of advanced chronic nephritis were studied from the standpoint of the parathyroid glands. In 1 case abundant mitoses were found in the glands, while in the other case none were to be seen. This led Pappenheimer and Wilens [35] to reinvestigate the question. They report that the weight of the parathyroid glands is related to age and sex in normal persons. Their data indicate clearly a considerable increase in the weight of the parathyroid glands in persons with advanced renal disease roughly proportional to the severity and extent of the lesions and to the intensity of the renal insufficiency. The functional significance of these changes is not wholly clear. It may be in some way compensatory for the disturbance in the excretion of inorganic phosphates in persons with renal insufficiency.

RENAL FUNCTION

The measurement of the urea clearance in children has been facilitated by the development of a micromethod for determination of the values for urea in the blood and an automatic collector of urine for use with infants. These have been described by Farr.[36] The determination of urea is made on as little as 0.25 cc. of blood.

Cullen, Nelson and Holmes [37] found the values for urea clearance of normal children to have a distribution and mean corresponding to those of normal adults. Observations were made on 78 children with

33. Albright, F.; Baird, P. C.; Cope, O., and Bloomberg, E.: Studies on the Physiology of the Parathyroid Glands: Renal Complications of Hyperparathyroidism, Am. J. M. Sc. **187**:49, 1934.

34. MacCallum, W. G.: Tumour of the Parathyroid Glands, Bull. Johns Hopkins Hosp. **16**:87, 1905.

35. Pappenheimer, A. M., and Wilens, S. L.: Enlargement of the Parathyroid Glands in Renal Disease, Am. J. Path. **11**:73, 1935.

36. Farr, L. E.: A Micromethod for Blood Urea and an Automatic Urine Collector for Urea Clearance in Infants, J. Clin. Investigation **14**:911 (Nov.) 1935.

37. Cullen, G. E.; Nelson, W. E., and Holmes, P. E.: Studies of Kidney Function in Children, J. Clin. Investigation **14**:563 (Sept.) 1935.

a history of hemorrhagic nephritis, and in this group the distribution and means corresponded with those of the normal group. When clearances were measured during the acute stage of the nephritis lower values were noted, but as a rule they returned to normal within a month after cessation of the acute symptoms. These findings emphasize the generally favorable outcome of hemorrhagic nephritis in children and the relative rarity of persistent functional impairment.

Van Slyke, Page, Hiller and Kerk [38] have made a further contribution to the study of urea clearance by the discovery that in persons with acidosis the clearance values are low if they are calculated from the urea and that they are normal if calculated from the urea plus ammonia. The authors believe that this indicates that the urinary ammonia is formed at the expense of the urea removed from the blood. In the formula $\frac{UV}{B}$ or $\frac{U\sqrt{V}}{B}$ the U should represent urea plus ammonia. The determination is simplified by the determination of the nitrogen content from reaction with an alkaline hypobromite. The routine procedure for this determination is described by Farr.[36]

MacKay and Rytand [39] made a statistical analysis of the relationship of the phenolsulfonphthalein test, the Addis ratio and the concentration of urea in the blood as a measure of the amount of functioning renal tissue in patients with Bright's disease. They state: "For certain clinical purposes the Addis ratio may be predicted as a percent of normal from the blood urea by dividing 1,755 by the blood urea concentration and from the phenolsulphonphthalein test by multiplying the percentage of dye excreted by 1." They observed that the ratio can be more accurately predicted by the results of the dye test than by the concentration of the blood urea. It was also noted that the excretion of dye and the concentration of urea in the blood may be well within normal limits until at least half the normally functioning renal tissue has been destroyed. An observation of somewhat similar nature had previously been made by Van Slyke in a comparison of the excretion of phenolsulfonphthalein with urea clearance.

Mosenthal and Bruger [40] have studied the value of the ratio $\frac{100 \times \text{urea nitrogen}}{\text{nonprotein nitrogen}}$ as an index of renal function, comparing it with Van Slyke's urea clearance, with which in general it agrees. Normal values are 44 or less, while with maximal impairment of function they exceed 80. The ratio rises and falls as function fails or improves.

38. Van Slyke, D. D.; Page, I. H.; Hiller, A., and Kirk, E.: Studies of Urea Excretion: IX. Comparison of Urea, Plus Ammonia, and of Nitrogen Determinable by Hypobromite, J. Clin. Investigation **14**:901 (Nov.) 1935.

39. MacKay, E. M., and Rytand, D. A.: Significance of the Phenolsulphonphthalein Test of Renal Function, Arch. Int. Med. **55**:131 (Jan.) 1935.

40. Mosenthal, H. O., and Bruger, M.: The Urea Ratio as a Measure of Renal Function, Arch. Int. Med. **55**:411 (March) 1935.

All types of renal disease have been studied. One wonders what values will be obtained in persons with severe hepatic disorders, in whom abnormal values for urea in the blood are sometimes noted. Apart from a few such questions it is anticipated that the Mosenthal-Bruger ratio may be very useful when only data on the chemistry of the blood are available, for instance, in cases in which the inability to collect urine renders determination of the urea clearance impossible.

Observations have been made by Page and Heuer [41] on the effect of renal denervation on arterial blood pressure and renal function in cases of essential hypertension. No effects on either were observed following bilateral denervation. Similar studies by these authors [42] were made on patients with nephritis. They found that denervation of the kidney, on one side as well as on both sides, caused a diminution in the amount of urinary protein in 4 of 5 cases of chronic nephritis. No changes in the urea clearance were noted following this procedure.

One of the outstanding papers of the year is that of Landis, Elsom, Bott and Shiels,[43] who draw attention to the important relation between sodium chloride and urea clearance in cases of severe renal insufficiency. These authors recall that in persons with intact kidneys in any of a number of shocklike states the chloride content of the plasma is low and the concentration of urea in the blood is high and that in such states the administration of sodium chloride raises the chloride content and lowers the urea content. The authors have noted also that in some cases of advanced renal insufficiency the administration of sodium chloride may have a similar effect when the chloride content is low. This is accomplished by slight increases in the urea clearance, which, though small, have a large cumulative effect in reducing azotemia. For instance, in 1 case the chloride content of the plasma was increased from 94 to 100 milliequivalents per liter, while the urea nitrogen content of the plasma fell from 154 to 32.8 mg., the creatinine content of the plasma fell from 7.2 to 5 mg. and the phosphate content of the serum from 7.3 to 4.9 mg. per hundred cubic centimeters. Landis also made use of a twelve or twenty-four hour specimen of urine for the determination of the urea clearance, because he found the values to vary less than in the one or two hour specimens usually employed. When these variations are eliminated it is possible to detect the small changes in function which the administration of sodium chloride effects.

41. Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, J. Clin. Investigation **14**:27 (Jan.) 1935.

42. Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on Patients Suffering from Nephritis, J. Clin. Investigation **14**:443 (July) 1935.

43. Landis, E. M.; Elsom, K. A.; Bott, P. A., and Shiels, E.: Observations on Sodium Chloride Restriction and Urea Clearance in Renal Insufficiency, J. Clin. Investigation **14**:525 (Sept.) 1935.

Book Reviews

Failure of the Circulation. By Tinsley R. Harrison, M.D., associate professor of medicine, Vanderbilt University School of Medicine. Price, $4.50. Pp. 396, with 22 tables and 60 illustrations. Baltimore: William & Wilkins Company, 1935.

In this rather short single volume Harrison has given the American medical profession the first concise but complete discussion of the significance of the failure of the circulation in its various forms. After a brief introduction in which he gives an interesting historical review of the outstanding contributions to the mechanism of heart failure, followed by a definition of the terms that he is to use in the subsequent chapters, he starts directly with the main discussion. He then takes up what he calls the three main methods by which the circulation fails, the hypokinetic, the hyperkinetic and the dyskinetic syndrome. By hypokinetic circulatory failure is meant an insufficient circulation, such as is found in shock and collapse. The hyperkinetic state signifies an overactive circulation such as occurs in certain nervous conditions, for example, neurocirculatory asthenia and hyperthyroidism. The dyskinetic syndrome indicates the "inefficient" circulation which is present in myocardial weakness or congestive heart failure. Although these terms are rather novel in their application to heart disease, the reader will quickly appreciate their significance and find that they help materially in understanding the nature of heart disease. The last section of the volume considers failure of the coronary circulation (angina pectoris and coronary thrombosis) as a problem that is different from congestive heart failure in many respects.

The outstanding characteristic of this volume is that it puts to physiologic and experimental proof many of the prevailing concepts concerning the nature of heart failure. In one sense it is a summary of an extensive study of this subject that Harrison has been conducting during the past ten years. He draws generously, however, on the work of many other investigators for support of his arguments. Throughout one sees an attempt to explain intelligently phenomena by direct observation of the pathologic physiologic condition of the patient or by experimental work on dogs. In this way light is thrown not only on the major problems in heart disease, such as dyspnea and edema, but on such questions as why the skin of a patient with one type of circulatory abnormality is warm and that of a patient with another type of this disorder is cold.

His main contribution is the discussion of congestive heart failure. He presents convincing evidence to support the proposition that congestive heart failure is not primarily concerned with the lack of output of the heart. It is rather a difficulty or inefficiency of ejecting the volume of blood that the heart puts out, which volume may not be greatly reduced from normal. He supports the theory of "backward failure" (back pressure) rather than that of "forward failure" (diminished output). He believes that dyspnea, edema, congestion and other disorders cannot be due to a diminished flow of blood to the tissues, but rather to a backing up of blood in those vascular areas which drain toward the failing chamber of the heart (in the lungs when the left ventricle fails and in the liver and extremities when the right fails). In this process of failing heart, dilation and increase in pressure proximal to the chamber involved are most important factors. Although an entirely different point of view still prevails in the minds of many of the present American and English authorities on the subject, Harrison's arguments are not new by any means. He merely has accumulated a mass of experimental evidence to support these conceptions.

In addition to the theoretical discussion, this book contains a great deal of practical advice concerning the diagnosis and treatment of heart disease. It therefore can be profitably read by both students and practitioners. In fact, in this

short volume there will be found a great deal of information that is new even to those specializing in cardiovascular disease. It is a most authoritative treatise on this particular subject, and it will repay one manyfold if it is read carefully.

Spontaneous Pneumothorax in the Apparently Healthy. By Hans Kjaergaard. Paper. Pp. 93, with 29 figures and appendix of 51 case histories. Copenhagen: Levin & Munksgaard, 1932.

This dissertation is a detailed study of spontaneous pneumothorax occurring in apparently healthy persons. For this condition Kjaergaard plausibly suggests the term "pneumothorax simplex," which is to be used for all cases of spontaneous pneumothorax occurring without demonstrable cause in healthy persons in whom no sign of tuberculosis can be found and in whom the disease takes an afebrile course without pleural effusion. In this class are also to be included cases in which the patients have a slight rise of temperature in the first week of the illness and cases in which the roentgenograms show the presence of an insignificant pleural exudate, too small to be made out on auscultation.

On the basis of facts obtained on observation of the sixty-one attacks seen in his own series of fifty-one patients and from a study of about two hundred cases reported by other authors, Kjaergaard arrives at important generalizations as to the etiology, pathogenesis, symptomatology, prognosis and therapy. The disease is due to the rupture of a valvular vesicle on the surface of the lung; photographs of such vesicles are given. In one instance the vesicle was seen in a remarkable roentgenogram, which is reproduced opposite page 39. Kjaergaard shows that this disease has nothing to do with active tuberculosis, so that these patients should be spared the loss of time and the expense of treatment in a sanatorium, as well as the fear of pulmonary tuberculosis. In partial pneumothorax the treatment is rest in bed for two weeks. In total pneumothorax, after two weeks of rest in bed cautious aspiration of air may be done. No after-treatment is necessary, and even in chronic pneumothorax that has persisted for more than a year the final outcome often is spontaneous recovery. In persistent cases, however, the intrapleural injection of 30 cc. of a 30 per cent solution of dextrose may be tried. In cases with severe dyspnea it is necessary to quiet the patient with morphine and to do immediate thoracentesis. Suction pumps are not essential in emergencies; one can connect the cannula with a rubber tube and aspirate with a syringe or with one's mouth. If there is hemorrhage, in desperate cases one may consider the possibility of thoracotomy and attempted ligation. In suffocating mediastinal emphysema with pneumothorax the treatment consists in repeated punctures, inhalation of oxygen and stimulation; it may be necessary to make a small median incision in the neck above the sternum and to express the subcutaneous air by stroking.

The book is written in excellent English. A curious feature, which is worth noticing, since it is sure to confuse American readers, is the use of the symbol $\div$ to denote subtraction or negativeness, as on pages 30 and 82. While this usage is the rule in Danish, it does not extend to all Scandinavian languages and is unfamiliar even to well read mathematicians. According to Cajori, it is deservedly obsolescent, and one wonders why, in this detail, the University of Copenhagen has not yet joined others in the effort to make mathematics the universal language that it ought to be. In every other respect this book is scholarly and admirable. It is well illustrated, and it deserves to be in the library of every one interested in diseases of the chest.

Das Extremitäten-, Thorax- und Partial-Elektrokardiogramm des Menschen. Eine vergleichende Studie. Bands I and II. By F. M. Groedel. Price, 25 marks. Pp. 358, with 334 illustrations; 200 plates. Dresden: Theodore Steinkopff, 1934.

This work consists of two volumes, a text and an atlas. The atlas contains two hundred excellent plates of electrocardiographic tracings illustrating the cases and discussions in the text.

The text is divided into two parts. Part I contains a general discussion of the physiology of heart muscle and a brief consideration of the principles of electrocardiography, leading up to a consideration of the partial electrocardiogram. The author considers the conventional electrocardiogram a superimposition of two distinct curves, a dextrogram and a levogram. By the aid of an indifferent electrode and small chest electrodes placed in the region of the lower part of the sternum and the left axilla, curves with constant characteristics are obtained in normal man and experimental animals. These tracings the author terms partial electrocardiograms and puts forth experimental and theoretical evidence to prove that they are dextrograms and levograms. Part II is concerned with the pathologic electrocardiogram. Groedel systematically considers various cardiac abnormalities as they affect the electrocardiogram. Deformities and changes in the partial electrocardiogram are used to localize cardiac damage and demonstrate changes not evident in the usual leads.

Evidence to prove that the partial curves are true dextrograms and levograms does not appear conclusive. Further experimentation on animals would seem most profitable. In the cases reported the electrocardiographic findings appear remarkably clear. However, sufficient postmortem confirmation of the ability of this technic to localize lesions, while most important, is lacking. Such confirmation, whether or not the curves are purely left-sided or right-sided, would establish an important diagnostic procedure and open up a new field in electrocardiography.

The book is of great interest to and should be read by all those engaged in electrocardiography.

Koronarinfarkt und Koronarinsuffizienz in vergleichender elektrokardiographischer und morphologischer Untersuchung. By Franz Büchner, Arthur Weber and Berthold Haager. Price, 12 marks. Pp. 104, with 131 illustrations. Leipzig: Georg Thieme, 1935.

This work is a comparative electrocardiographic and morphologic study of infarction and insufficiency of the coronary vessels. The text consists of a short discussion of infarction in the various branches, followed by a consideration of insufficiency of the coronary circulation in relationship to aortic syphilis, marked anemia, coronary sclerosis and hypertension. Disseminated necrotic areas resulting from acute coronary insufficiency are described and histories of cases presented; in two cases there were changes in the right ventricle. Electrocardiographic findings resulting from these changes are outlined. Pericarditis and its electrocardiographic changes are also taken up.

The illustrated case reports are excellently arranged, with a photograph of the heart, sectioned to show the gross pathologic picture; a portion of the electrocardiogram, and a diagram of the coronary circulation indicating the pathologic changes present. The important clinical facts are given, with an interpretation of the electrocardiogram, a verbal description of the cardiac pathologic changes and finally an analysis of these findings. The diagrams, photographs and tracings are excellently done and so arranged that those familiar with electrocardiography but with little knowledge of the German language will have no difficulty in understanding the ideas conveyed.

The Q_1-T_1 and Q_3-T_3 types of curves are confirmed as indications of anterior and posterior infarction, respectively. The interpretations given under coronary insufficiency are more often subject to variation. While all will not agree with the authors' correlation of the electrocardiographic findings and the pathologic changes of the coronary vessels, the data are so completely and so clearly given that one may evaluate the findings and interpret them himself. In case eleven, for example, the reviewer was led to different conclusions.

The reviewer can only praise the method of presentation of the data and the thoroughness with which it has been carried out.

The Principles and Practice of Urology. By Frank Hinman, M.D., clinical professor of urology at the University of California Medical School. Price, $10. Pp. 1111, with 513 illustrations. Philadelphia: W. B. Saunders Company, 1935.

The beginning of a recent book notice in *The Journal of the American Medical Association* won this reviewer's heart: "This book heralds the return of the larger and more comprehensive textbooks." For some years there has been a lack on our side of the Atlantic, at least, of comprehensive medical textbooks written by a single person whose knowledge of a given subject is broad enough to permeate an entire book, whose literary style is well enough sustained to make whatever he writes of interest and whose enthusiasm is contagious enough to infect an unsensitized reader.

Hinman's book is good. First, it is well written, so that even a physician can easily perceive something of the charm of urology. Second, it is well illustrated, so that matters highly technical to the uneducated mind and eye become fairly clear. Third, it has a good index, so that at an instant's notice one can familiarize oneself with anything in the field of urology from the aberrant vas of Haller (a structure which many physicians do not know when they meet it) to the zones of Head.

The prefatory *apologia* describes the personality of his book nicely. It started, apparently, with the humble object of presenting the principles of urology in practical form to the medical student and the physician in general practice; it ended neither a primer nor a compendium, but a first-class textbook written laboriously and earnestly in an attempt to instruct the medical student, to cover the field of urology for the general practitioner and to serve as a reference book for the complete urologist.

Those who dislike the current fashion of many-authored textbooks will welcome this one with eagerness. It is a fine achievement.

Biochemistry of Medicine. By A. T. Cameron and C. R. Gilmour. Second edition. Price, $6. Pp. 518, with 31 illustrations. Baltimore: William Wood & Company, 1935.

The appearance of this second edition two years after the publication of the first indicates that the book has been well received by the medical profession. This is easily understandable. The authors have taken great care in the preparation of the work to make it readable, to make it interesting to the physician in general practice and to reduce to a minimum the chemical features of the text. In other words, the book has been prepared with the definite intention of making available for the practitioner of medicine an explanation for the various biochemic reactions that occur in health and disease. The results speak for themselves.

It is interesting to note that in this second edition it has been necessary largely to rewrite the section on the endocrine glands, and the section on the vitamins might well have been subjected to extensive revision, an interesting observation on the tremendous strides that are being made in the advancement and knowledge concerning these two phases of medicine. Particularly to be stressed is the excellent summary at the end of each chapter, which should be read before the main features of that chapter, because in this way the reader gets an excellent general picture in which the details are filled in by the material which is elaborated in the section which precedes the summary. Also to be commended is the excellent list of references at the end of each chapter. As no attempt has been made, and in fact it would be impossible, to include all references, it might have been of some value to the reader who is not intimately acquainted with biochemistry had the authors been more selective in the use of references and instead of including from 100 to 115, not all of which are outstanding, had utilized one third of the number, as references to the papers that are really worth while and of current importance.

Corazón y vasos. By Dr. Pedro Cossio, chief of the section on cardiology of the Argentine Institute for Diagnosis. Pp. 385, with 266 illustrations and diagrams. Buenos Aires: "El Ateneo," Librería científica y literaria, 1935.

This book gives an interesting description of the various diagnostic methods now available for the recognition of cardiovascular diseases. The first chapter describes the anatomy and pathologic physiology of the circulatory system. Next is a chapter on the importance of an adequate history, and this lays due emphasis on the proper interpretation of symptoms. Next is an excellent account of how to examine the heart, of the technic of auscultation, percussion and palpation. Much of the remainder of the volume deals with the more mechanical diagnostic methods in general use; the electrocardiogram, the use of the roentgen rays or fluoroscope, sphygmomanometry, arteriography and methods for studying the capillaries. Finally there is a long chapter of fifty-five pages which discusses in detail the interpretation of electrocardiographic tracings.

The charm of the book lies in the manner in which it is written. It is written simply and is well illustrated so that each point which the author wishes to emphasize is clearly set forth. There is no reference to the current literature, the author evidently preferring to have familiarized himself with the ideas of other investigators and then to write from his own point of view. The result is a logical presentation, unusually readable and expressing a sound conception of heart disease. The book has been compiled for the benefit of general practitioners who are interested in modern cardiology. They should appreciate it.

Die Electrocardiographie und andere graphische Methoden in der Kreislaufdiagnostik. By Prof. Dr. Arthur Weber, Direktor des Balneologischen Universitäts- Instituts, Bad Nauheim. Second edition. Paper. Price, 15.60 marks; bound, 16.50 marks. Pp. 180, with 129 illustrations. Berlin: Julius Springer, 1935.

To those interested in graphic methods of studying the circulation this work will furnish a good review of the subject. Weber describes the method of recording heart tones, arteriograms, venous curves, cardiograms and electrocardiograms. All the methods are described in considerable detail. Several varieties of electrocardiograph in use in continental Europe are described. A description of those in common use in America is lacking.

In discussing the different diseases of the circulatory system records are shown and described in which the various tracings are synchronized and superimposed. For example, in the discussion of disease of the mitral valve, a photograph of the heart tones, the venous and arterial curves and the electrocardiogram may be studied all on the same record. The various cardiac arrhythmias are discussed in a similar fashion, as are alternation of the pulse, gallop rhythm and disease of the coronary vessels. Only the conventional three leads of the electrocardiogram are given. No mention is made of leads IV, V and VI that are being discussed in this country at the present time.

There is nothing new in the work, but existing knowledge is well correlated and beautifully set out. An excellent bibliography is a part of the work.

Traité de gastroscopie et de pathologie endoscopique de l'estomac. By François Moutier. With a preface by Prof. P. Duval. Price, 120 francs. Pp. 347, with 89 figures and 24 plates. Paris: Masson & Cie, 1935.

This monograph, an excellent review of gastroscopy, is divided into three parts. The first part contains a dissertation on the history of the instruments and methods, the anatomy of the stomach, instrumentation, orientation and contraindications; the second part deals with the physiologic and morphologic features of the normal stomach as seen gastroscopically, and the third part includes a discussion of the various diseases of the stomach, functional as well as organic.

Moutier presents the material clearly and briefly. He correlates the normal and pathologic, emphasizing a preliminary appreciation of the normal. He appreciates that gastroscopy supplements other methods of clinical study and should be employed when indicated. He shows how the gastroscopic investigations can be correlated with the patient's history and the results of physical examination, roentgen studies and other laboratory studies. Many good roentgenograms and gastroscopic plates are included in the monograph to illustrate findings in various disorders of the stomach.

The treatise is a good collective source of information of the French literature on gastroscopy.

News and Comment

FIRST INTERNATIONAL CONFERENCE ON FEVER THERAPY

The first international meeting on fever therapy will be held in New York in September 1936. The conference will aim to collect and crystallize available data regarding the use of fever induced by physical and other agencies as a therapeutic procedure. Therapeutic, physiologic and pathologic phases of fever will be discussed. Those interested in participating are requested to make early application to the secretary, Dr. William Bierman, 471 Park Avenue, New York. It is planned to translate abstracts of all the papers into French, English and German. Manuscripts and abstracts should be in Dr. Bierman's hand not later than June 1, so that printed copies of the translations may be available for the conference.